JUNE, 1950

The Review of Gastroenterology

OFFICIAL PUBLICATION

NATIONAL GASTROENTEROLOGICAL ASSOCIATION

An Appraisal of Current Methods for the Treatment of Portal Hypertension

The Effect of Resection of the Sympathetic and Parasympathetic Innervation of the Stomach upon Gastric Acidity

Facts and Problems of Hepatitis

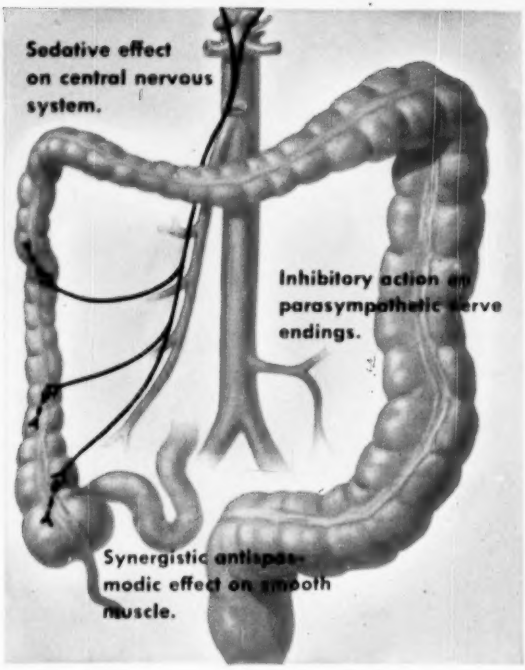
Blood Test for Cancer

●

Fifteenth Annual Convention

New York, N. Y., 9, 10, 11 October 1950

VOLUME 17 NUMBER 6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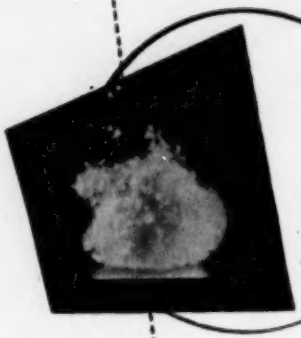

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The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

VOLUME 17 JUNE, 1950 NUMBER 6

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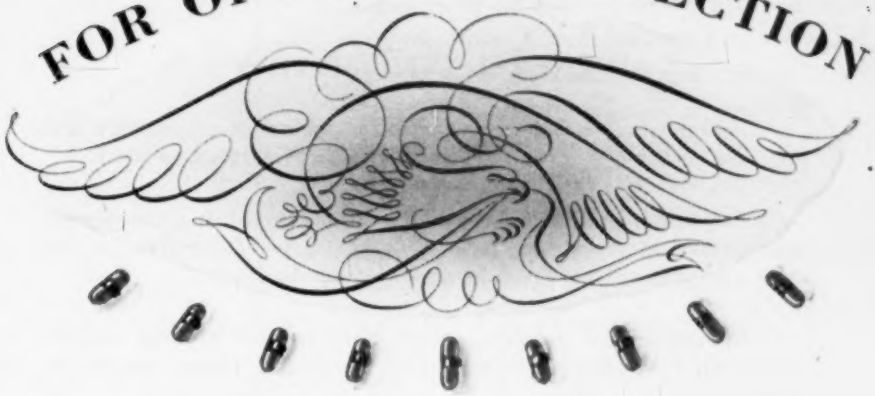

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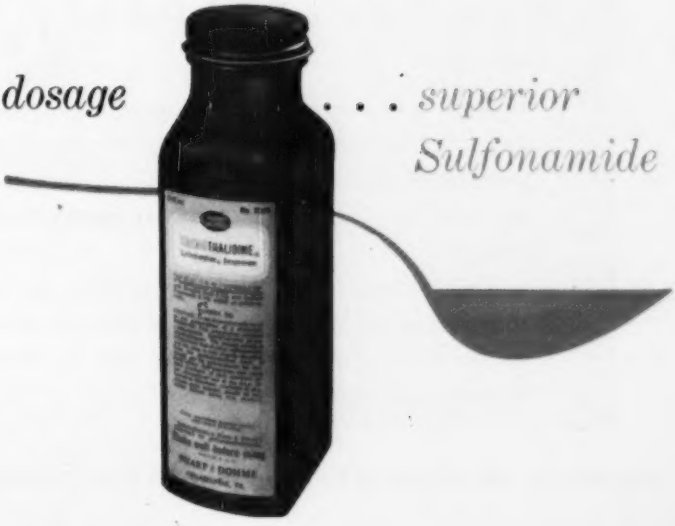

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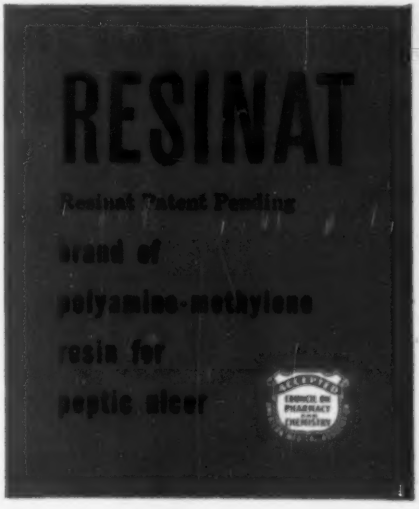

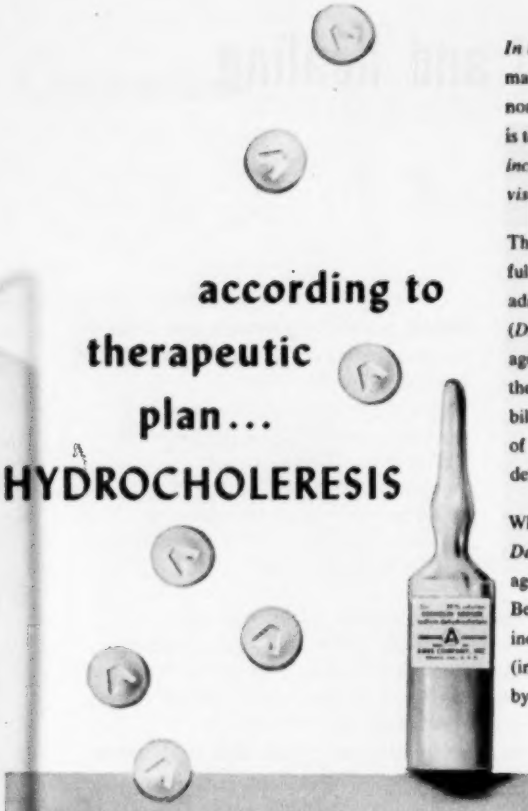

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AN APPRAISAL OF CURRENT METHODS FOR THE TREATMENT OF PORTAL HYPERTENSION*†

C. STUART WELCH, M.D.**
and
ALLAN D. CALLOW, M.D.††
Boston, Mass.

Whenever numerous technics are available for the treatment of a disease, it is usually axiomatic that no one of them is completely satisfactory. Some progress has been made in the treatment of portal hypertension but the problem is far from solved. Unfortunately the nature of the fundamental underlying disease often precludes the possibility of accomplishing more than palliation in the majority of instances. The present interest in surgery for portal hypertension was stimulated by the work of Blakemore and his colleagues when, in 1945, they published their work on its operative treatment by the method of shunting the high pressure portal blood into the lower pressure systemic venous system by means of large intraabdominal venous anastomoses. They demonstrated that the operations of Eck's fistula and anastomosis of the splenic vein to the renal vein could be carried out in patients with portal hypertension without incurring prohibitive operative mortality rates[1]. These operations had been done by French and German surgeons around the turn of the century but were abandoned because of the great risk which surgery of such magnitude carried at that time. Progress in modern surgery has again made these operations feasible. Other surgeons have directed their attention to the development of new and original methods of approaching the problem of surgery for patients with portal obstruction and it is the purpose of this communication to comment on the rationale of some of the procedures being tried in this group of patients with this serious complication resulting from blocking of the return of portal blood to the heart.

The Mechanism and Significance of Portal Hypertension

The portal venous system which drains the abdominal viscera may be blocked by direct impingement on the portal vein or its tributaries, or the portal venous

*Read before the Fourteenth Annual Convention of the National Gastroenterological Association, Boston, Mass., 24, 25, 26 October 1949.

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system in the liver may become constricted by the fibrotic changes which accompany disease of the liver. There are, therefore, two general sites of obstruction to the portal flow, extrahepatic and intrahepatic. Back pressure in the valveless portal system is rapidly transmitted to all the tributaries and produces in many instances a congestive splenomegaly followed by an enlargement of the normal small collateral routes between the portal and systemic veins. The hypertension created by obstruction in the portal bed is thereby transmitted to the collateral routes. Large varices are formed in the regions where collateral veins are present beneath the mucous membrane and here massive hemorrhage may occur producing exsanguination and death. Submucosal varicosities are found in the cardiac end of the stomach, in the esophagus and in the anorectal region. Unfortunately, it is impossible to successfully operate during hemorrhage from esophageal varices and the mortality is extremely high when these patients bleed. Hemorrhage is much more serious in patients with intrahepatic portal bed block from cirrhosis of the liver not only because the exsanguination is usually greater but these patients are generally older and are debilitated by advanced liver disease. Blakemore states that the patient with cirrhosis of the liver and portal hypertension who has bled from esophageal varices has only a fifty per cent chance of being alive one year after his primary hemorrhage[2]. Linton, at the Massachusetts General Hospital, states that a 36 per cent mortality rate followed bleeding from rupture of esophageal varices in the group of patients studied by Shull in that institution[3]. Others have reported similarly on the seriousness of gastrointestinal hemorrhage in patients with cirrhosis of the liver[4]. Bleeding is so often fatal in patients with portal hypertension that any reasonable approach to the problem of its control should be carefully considered and in most cases experimental operative procedures are justified if they have a fair degree of reasonability.

The site of block and fundamental pathologic process producing portal hypertension is a most important consideration in prognosis and in the surgical treatment for the individual patient since it is obvious the patient with cirrhosis of the liver is a much poorer risk for surgery. Indeed, liver function is usually so poor as to contraindicate any attempt to ameliorate the factor of portal hypertension in the majority of patients with cirrhosis of the liver. In the general course of hospital experience, 85-90 per cent of patients who have portal hypertension will be found to have cirrhosis of the liver since extrahepatic obstructions are relatively uncommon lesions. These patients need special evaluation before they can be considered for surgery. Those individuals who have obstruction outside the liver are more fortunate in having a normal liver function and, indeed, they may be sometimes completely cured by surgical intervention. The types of extrahepatic lesions blocking the portal system have been classified by Linton[5] into congenital and acquired types. Obliteration of the portal vein and stenosis and atresia of the portal vein represent the congenital varieties. Acquired obstruction results from thrombosis of the portal venous system and from abdominal injury when it is followed by cicatrical obstruction of veins. Tumors and other masses may also

impinge on the venous return. In almost all cases the differentiation between those patients with extrahepatic obstructive lesions and intrahepatic disease can be made before operation by studying liver function. An estimation of the liver function in all patients with splenomegaly and esophageal varices is essential before any thought of surgery be entertained. Patients with cirrhosis of the liver may show very few stigmata of their disease and, in certain types, relatively good hepatic parenchymal function exists in the presence of a high degree of periportal fibrosis which has produced sufficient portal hypertension to result in varices and hemorrhage. Hepatic function tests, however, will always disclose sufficient disturbance of liver function to identify the liver as the site of the fundamental pathology.

In Table I we have illustrated the important differential laboratory findings in two patients both of whom had esophageal varices, splenomegaly, and had had massive hemorrhage from the gastrointestinal tract. The values obtained for the

TABLE I

COMPARISON OF LABORATORY STUDIES IN TWO PATIENTS WITH PORTAL HYPERTENSION

	Obliteration of Portal Vein (extrahepatic obstruction) C. D., male, age 17 years	Cirrhosis of Liver (intrahepatic obstruction) R. L., female, age 12 years
Liver Function Studies		
Bromsulphthalein Retention	5%	40%
Serum Bilirubin	1 mg.%	.5 mg.%
Total Protein	6.5 grams%	5.9 grams%
Albumin	4.3 grams%	2.3 grams%
Globulin	2.2 grams%	3.6 grams%
Total Cholesterol	156 mg.%	83 mg.%
Cholesterol Esters	75% of total	61% of total
Blood Picture		
Red Blood Cells	3,280,000	2,720,000
Hemoglobin	10.7	3.8 grams
White Blood Cells	2,000	1,750
Platelets	137,760	816,000

liver function in the case of the patient who had obstruction of the portal vein were normal whereas in the patient who had had a previous hepatitis there was marked derangement in the values. Particularly notable was the higher degree of retention of bromsulphthalein and the reduction in the serum albumin in the patient R. L. who had cirrhosis of the liver. Both of these patients were operated upon and biopsies of the liver corroborated the clinical diagnoses; splenectomy and splenorenal anastomosis were done in both cases with immediate good results. While it is possible to determine that the site of the block is in the liver in most instances, it is difficult to say much about the site of block in extrahepatic obstruction before surgical exploration or postmortem examination. At operation it is possible to make pressure studies in the various tributaries of the portal vein and while the exact site may be found in many instances the site and exact nature of the obstructing lesion can only be a matter of conjecture.

The second complication of portal hypertension in addition to massive hemorrhage from varices is hypersplenism or the disturbance created by abnormal influence of the spleen on the blood and blood-forming organs. Banti was the first to

describe the anemia associated with congestive splenomegaly and the syndrome of portal hypertension with splenomegaly and anemia often goes by his name. The exact mechanism by which the spleen produces these unfavorable changes in the hematologic picture is not known but it would appear that whenever the spleen becomes enlarged from almost any cause, it may suddenly begin to increase its normal function. This is manifest in some cases by hemolytic activity and, in others by inhibiting the maturation and escape of the cellular elements of the blood from the bone marrow. In cases of congestive splenomegaly resulting from portal hypertension it is not unusual to see splenic anemia and, indeed, various other cytopenias. Leucopenia is frequently found. Thrombocytopenia may exist and in some cases a selective neutropenia may result. In Table I the effect of this over-action of the spleen may be seen in the blood picture of both the patient with

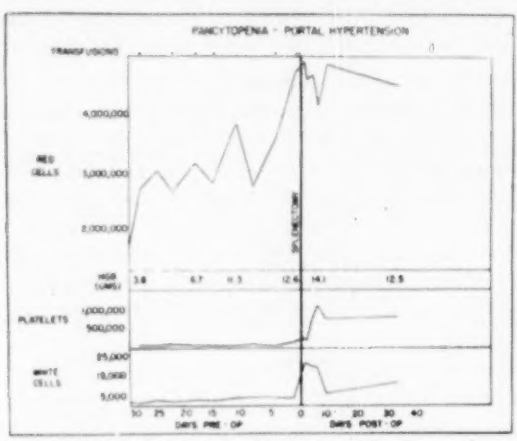

Fig. 1—The pancytopenia which existed before splenectomy and splenorenal anastomosis in the case of a patient with portal hypertension, splenomegaly, and hypersplenism and its correction by the removal of the spleen. The increase in hemoglobin values and red blood cell count before operation are the result of blood transfusions as indicated.

extrahepatic portal obstruction and the one with cirrhosis of the liver. The value of splenectomy in the treatment of this aspect of congestive splenomegaly lies in the relief obtained from hypersplenism and in most cases the blood picture rapidly returns to normal.

In Figure 1 we have graphically indicated the pancytopenia which existed before operation and the restoration of the blood picture to normal which occurred after splenectomy and splenorenal anastomosis in a patient with congestive splenomegaly and cirrhosis of the liver. The improvement in this patient's blood counts before operation by transfusions could not be sustained but since splenectomy and splenorenal anastomosis, the anemia, leucopenia, and thrombocytopenia remains corrected. Bone marrow studies in this patient before operation showed it to be hyperplastic and therefore, there was good evidence that splenectomy would correct this profound hematologic disturbance. We may see then that two factors

often produce anemia in these patients with portal hypertension: massive hemorrhage and anemia of splenic origin. The removal of the spleen as we shall point out later has long been used for the correction of the anemia of congestive splenomegaly and is an aspect of the treatment of portal hypertension that demands attention since the patient may succumb from it, particularly if leucopenia and neutropenia coexist and infections supervene.

Surgical Procedures Used in the Treatment of Portal Hypertension

In Table II the important procedures which have been tried with varying success in attempts to decrease the incidence and seriousness of gastrointestinal hemorrhage of portal hypertension origin are listed. All of the major operative procedures must be done in intervals between bleeding episodes and in general are of sufficient magnitude to require that the patient be in the best possible condition for surgery. Patients with cirrhosis of the liver are unfortunately not good

TABLE II

Operative Procedure for the Control of Bleeding in Portal Hypertension

Procedure	*Rationale*
1. Omentopexy	Establishment of new collateral routes
2. Mediastinotomy with packing	Establishment of new collateral routes
3. Splenectomy	Reduction in portal bed circulatory volume, relief of hypersplenism, and reduction of communications with esophageal varices
4. Ligation of splenic artery	Reduction in portal bed circulatory volume
5. Injections of esophageal varices	Sclerosis of varicosities
6. Tamponade of esophageal varices	Obliteration of varices by pressure (temporary)
7. Esophagogastrectomy, total gastrectomy	Excision of the varicosities
8. High gastric resection	Reduction of gastric acid erosion of esophagus
9. Venous shunts	
a) Splenectomy with splenorenal anastomosis	Reduction in portal bed circulatory volume, relief of hypersplenism; Reduction in portal venous pressure
b) Portacaval and other venous shunts	Reduction in portal venous pressure

candidates for many of the operations proposed and a careful selection of patients must be made in order to avoid surgical mortality rates which exceed patients' chances of living with nonintervention.

The Establishment of New Collateral Routes:—The operation of omentopexy proposed by Talma[6] and popularized by Morison[7] at the turn of the century represented an attempt to establish new vascular channels between the omentum (and portal bed) and the systemic venous system. Omentopexy has been used with the hope that these new communications may reduce portal pressure and thereby lessen gastrointestinal hemorrhages and that ascites may be relieved by this procedure. Today the operation has been abandoned with the advent of the large shunt operations. The operation of omentopexy produces feeble communications and probably no more extensive or better ones than the natural adhesions

of the omentum to the upper surface of the liver, diaphragm or abdominal wall which are usually found to have occurred in patients with advanced cirrhosis.

Som and Garlock[8] have more recently proposed another plan for the promotion of new vascular channels to relieve high pressure in esophageal varices. In their operation, posterior mediastinotomy is performed by incision in the neck and the periesophageal area packed with gauze down to the arch of the aorta for a period of time. It is assumed that larger periesophageal vascular channels thereby result from the formation of granulation tissue stimulated by packing and thus relieve the tension in the more vulnerable submucosal veins. The rationale of this procedure is not entirely clear and there is an insufficiency of data on the results of this operation to assure its value at this time.

Splenectomy and Ligation of Splenic Artery:—The amount of blood which the circulation through the spleen contributes to portal blood volume has been variously estimated to be from 20 per cent to 40 per cent of the total and a beneficial effect of splenectomy in portal hypertension with congestive splenomegaly has been ascribed to the reduced portal blood flow which the operation accomplishes. In addition the well-established routes from the spleen to the gastric veins are severed and perhaps a reduction in effective communications with the esophageal varices results.

Banti suggested splenectomy for the relief of the syndrome which he described but the largest early group of patients with "Splenic Anemia" treated by splenectomy was reported in 1919 by W. J. Mayo[9]. More recently Pemberton and Kiernan[10] have reported their results in the treatment of 208 patients with splenic anemia most of whom we must presume had portal hypertension of either the intra- or extrahepatic type although no data is given on this aspect of diagnosis in their group. Their report presented a follow-up study of patients five years or more after splenectomy. The survival rate was 54.8 per cent for five years and 42 per cent lived ten years after splenectomy. Unfortunately, these authors do not give the incidence of varices in their patients nor do they indicate the survival rate for those who had varices at the time of splenectomy. One hundred seventy-three of their 208 had sustained one or more hemorrhages before operation, however. These results seem to indicate a solid value for splenectomy as a single procedure in patients with splenic anemia and bear out the general experience of many surgeons that splenectomy is of definite, if only temporary, value in portal hypertension.

Opinion varies as to the ultimate value of splenectomy particularly in cases of cirrhosis of the liver with portal hypertension and hemorrhage but it is without doubt a valuable operation in selected cases of portal obstruction as a single measure. The value of splenectomy in the treatment of hypersplenism, if it exists, has been discussed and represents another justification for the operation. One must take into account the severity of the liver disease in those patients with cirrhosis, since their generally poor condition may prohibit splenectomy on the grounds of its high mortality. On the other hand, patients who are good candi-

dates for splenectomy should have the added value of a simultaneously performed splenorenal anastomosis. No matter how important an addition the shunt procedure may be, however, the increment which splenorenal vein anastomosis has added to simple splenectomy in the treatment of these patients has not been exactly established while the importance of splenectomy cannot be denied. The subject of splenorenal anastomosis with splenectomy will be discussed more fully later. In some patients with portal hypertension, congestive splenomegaly and severe liver disease, an operation of the magnitude of splenectomy has been found to incur a mortality rate as high as 40 per cent[11]. For those patients some degrees of relief may be obtained by the operation of ligation of the splenic artery. Blain[12] was apparently the first to report on the use of ligation of the splenic artery in 1918. It has been employed by others and more recently has been recommended by Cole and his associates[13]. The latter group found that interruption of the arterial supply to the spleen was followed by gradual atrophy of the organ and in effect produced a functional splenectomy. We have found no occasion to employ this procedure but it should be kept in mind for particular cases and as suggested by Linton may be a valuable procedure preliminary to splenectomy and splenorenal anastomosis in very ill patients or may be considered at the time of massive hemorrhage as a means of arresting hemorrhage from varices.

Direct Treatment of Varices

Sclerosis:—The injection treatment of varicose veins has been applied to the treatment of esophageal varices. Crafoord and Frenckner[14] reported their technic in 1939 using a sclerosing solution of quinine with direct injections of the varices performed with a specially designed needle through an esophagoscope. One patient so treated had been followed three years without hemorrhage. Moersch[15,16] of the Mayo Clinic has had the largest experience with this technic having treated 22 patients. Over one-half of his patients had had no bleeding three to seven years since the completion of their course of injections. Since extension of varices in the stomach is frequently the case it would seem impossible to be complete in eradicating all possible bleeding points. Nevertheless, this technic would seem to have considerable merit from the reported results and has the advantage of being carried out at low risk to the patient in the hands of experienced endoscopists. The number and frequency of esophagoscopic procedures is somewhat of a trial to the patient and many will not carry on with the course of treatments necessary.

Tamponade:—In the phase of acute hemorrhage from esophageal varices tamponade by direct pressure using various types of distensible balloons mounted on gastric tubes has been advocated[17]. How effective mechanical occlusion of these veins by pressure during active bleeding will prove to be remains to be seen as the result of more experience. The odds are somewhat against its success on two scores: first, there is no way of localizing the exact site of hemorrhage for application of the pressure balloon, and secondly, it might be questioned that distention of the esophagus within safe limits is effective in obliterating the varices. It is conceivable, moreover, that the trauma induced by tamponade might cause more

bleeding. On the other hand, this method should have an extensive trial for it represents the only direct approach to stopping hemorrhage that can be used in these patients and, as has been pointed out before, the mortality rate is so high even with the best of supportive therapy that any reasonable technic should be tried.

Resection:—Phemister and Humphreys[18] have advocated resection of the esophagus and stomach, excising the area containing varices at an elective time between hemorrhages. They have performed total gastrectomy in one case and resection of a portion of the lower esophagus and upper part of the stomach in another. Both patients survived the operations but the follow-up reported has been of insufficient duration to establish the value of these procedures. This approach is certainly direct and merits consideration since complete removal of these veins eliminates the dangerous site of the collateral circulation from which the fatal hemorrhages occur. In projecting esophagogastrectomy for patients with portal hypertension, however, it must be kept in mind that the risk of this operation may be prohibitive in those with advanced liver disease. Another factor limiting enthusiasm for these resections is the knowledge of the extent of varices which in some cases reach above the arch of the aorta and into the stomach making complete removal difficult. How fast new varices may appear after esophagogastric resection is another unknown which will influence the final acceptance of these procedures. At present we must consider these operations experimental but well conceived with respect to the problem at hand but unlikely to compete with shunt operations as a first procedure in most patients.

Prophylaxis Against Erosion:—How much the factor of peptic ulceration of the esophagus by gastric juice may play in the initiation of hemorrhage by erosion of the esophageal varices is difficult to say but that it may be important represents a new concept proposed by Wangensteen and Baronofsky[19]. Their thesis presumes that peptic ulceration of the esophagus is more common than generally believed and that varices in the esophagus probably would not rupture by hydrostatic pressure alone in the majority of instances. It is presumed that impairment of nutrition of the mucous membrane of the esophagus, stomach and duodenum due to venous pooling lowers the resistance in these areas and makes them easy prey to the gastric digestive juices. If the acid peptic factor of gastric secretion were important in the causation of erosions of the esophagus the operation of extensive gastrectomy might be a rational prophylaxis against hemorrhage. Additional theoretical benefits which are attributed to a large gastrectomy are the isolation of the esophagus from the portal circulation and the reduction of blood flow in the portal system which should follow excision of this organ. The fact that reduction of portal bed circulating volume occurs after excision of any viscera has not been entirely established, however. The experimental work on this subject of esophageal erosion from acid peptic digestion is also not conclusive since portal hypertension similar to that seen in man with esophageal varices cannot be reproduced in dogs. Wangensteen and associates have performed large gastric resection (90 to 100 per cent)

on 8 patients having esophageal varices and portal hypertension. The mortality rate has been 50 per cent and the follow-up period has been short in the survivors; nevertheless, this procedure has merit in design and should be carried out in other patients for further evaluation.

Venous Shunts Between the Portal and Systemic System

The most direct attack on reducing high pressure in the portal system would seem to be by shunting the blood from the portal or splenic vein into the vena cava

Fig. 2—Completed end-to-side anastomosis of the splenic vein to the renal vein. The exposure has been made by a combined abdominothoracic incision which cuts across the left rectus muscle and extends up over the 9th rib. The 9th rib is resected and the diaphragm opened. This exposure, as described by Linton, greatly facilitates the operative procedure of splenorenal anastomosis.

or one of its large tributaries. Pressure in the vena cava at the level of the renal veins is low (4 to 8 cm. of water) and should absorb and reduce the high portal pressures of 30 cm. to 60 cm. which are present in portal obstruction. Although portacaval shunts were performed in the early part of this century the rationale was not clearly understood nor the operative procedure established on a safe basis until the work of Blakemore and his associates in 1945. In his latest communication Blakemore[20] gives his experiences with shunt operations in 62 patients with portal hypertension; 18 of these patients had portacaval anastomosis and in 47 spleno-

renal anastomosis was performed; 3 had both procedures done at different times. The mortality rate for this surgery in his hands has been much under the expected risk from death by exsanguinating hemorrhage which these patients face. Linton[5] has likewise demonstrated that the shunts between the splenic and renal veins may be done with relatively low mortality. The indications for operation, selection of procedure and results have been carefully studied by these investigators.

It is generally conceded that the large anastomotic shunts of the splenorenal or portacaval variety are superior to small vein anastomosis both from the standpoint of the larger volumes of blood diverted and the better chance of the anastomoses remaining open. Anatomic factors such as the site of obstruction and whether or not splenectomy has been performed previously are determining factors in the selection of the site of shunt for each case. Obviously portal vein-vena cava anastomosis cannot be useful in instances of extrahepatic portal obstruction in the splenic vein, nor can it be done in obliterative disease of the portal vein. If there is no evidence of liver disease before operation the problem of determining the site of obstruction usually remains for solution at surgical exploration.

In our opinion, patients with congestive splenomegaly should have splenectomy and splenorenal anastomosis; this operation is technically more easily performed and accompanied by lower mortality rates than the portacaval anastomosis. In addition, in theory at least, it accomplishes reduction in circulating portal blood volume by splenectomy as well as portal decompression. An added benefit of this operation is the elimination of hypersplenism so often found in these patients. We are in agreement with Linton that splenorenal anastomosis should be done in cases of splenic anemia instead of splenectomy alone whenever possible. His technic of end-to-side suture anastomosis of the splenic to renal vein with preservation of the kidney using the abdominothoracic approach is the procedure which we have latterly carried out with best results (See Fig. 2). Another advantage of splenorenal anastomosis is that it is applicable to almost all types of portal bed obstructions.

Anastomosis of the portal vein with the vena cava above the renal veins produces a larger shunt it is true, but in our hands, and in the experience of others the operation is more difficult and accompanied by higher mortality. The reason for the greater risk accompanying portacaval anastomosis is not entirely because the dissection and procedure of anastomosis is more difficult and hazardous but equally because this operation is performed almost exclusively on patients with cirrhosis of the liver who are much poorer risks than the general run of patients upon whom splenorenal anastomosis has been possible. It is not, in our opinion, an operation to be elected as a first procedure in preference to splenorenal anastomosis, but it is reserved for those patients with cirrhosis of the liver and intrahepatic portal bed block who have had previous splenectomy or splenectomy and splenorenal anastomosis with recurrence of bleeding. The surgeon is, therefore, always dealing, in this group requiring portacaval shunt, with patients with liver disease, with more advanced debilitation than in the case of the group selected for

splenorenal anastomosis, many of whom have the less serious lesion of extrahepatic block.

In our experience anastomosis of the portal vein to the vena cava has been accompanied by a 50 per cent mortality rate among 6 patients all of whom had cirrhosis of the liver and had had splenectomy in the past. The mortality rate for splenorenal anastomosis has been 25 per cent (2 deaths in 8 operations). All of our patients except one who have had a splenorenal anastomosis likewise were individuals with cirrhosis of the liver. These results bear out the experience of others that the operative mortality rates are higher in the group with cirrhosis than in those with extrahepatic lesions. Patients with too far advanced liver disease were operated upon in our early experience as borne out in our group upon whom we performed portacaval anastomosis by the fact that large ascitic accumulations at the time of operation were present in two cases with poor liver function. The three patients surviving operation lived only 3, 6 and 18 months after operation further indicating the advanced disease present in this operated group. All of our patients surviving splenorenal anastomosis are alive from 3 months to 2 years postoperatively without recurrence of hemorrhage. We attribute the better results in these patients largely to the fact that they were operated on earlier in their disease.

Selection of Patients for Portacaval Shunts

Blakemore has adequately discussed the selection of patients who may be reasonably undertaken for shunt operations and we have little to add to it except to accentuate the point that low plasma protein values, ascites and other evidence of a functionally incapacitated liver tend to exclude patients from the group acceptable for surgery unless liver function rapidly improves on medical management. Patients with extrahepatic obstructions and no liver disease and those with cirrhosis of the liver and marked hypertension but with fairly good cellular function of the liver are the most promising candidates. We believe that patients with ascites and low proteins should not be operated upon, even though they have varices and have bled, unless medical treatment relieves the ascites and improves liver function. The shunt operations, it must be pointed out, do nothing but reduce portal pressure and have no direct beneficial effect on liver function itself. It is our belief that portal hypertension contributes little to the formation of ascites and that shunt operations have no application to the treatment of ascites. When the principal problem is marked liver dysfunction, the patient who does not improve on medical treatment will die from liver disease as soon or sooner than from the portal hypertension and hemorrhage. He will in any event be a prohibitive risk for a shunt operation. The age of the patient, likewise, affects the operative mortality and patients beyond sixty years of age with cirrhosis of the liver are usually much poorer risks.

Comment

Of the variety of procedures used in the treatment of patients with portal hypertension, splenectomy with simultaneous splenorenal anastomosis would seem

to offer the best chance of ameliorating fatal gastrointestinal hemorrhages by its reduction in portal venous pressure. When the spleen has been removed at a previous operation other portacaval shunts should be considered.

In considering patients with portal hypertension for surgery each one must be individualized, for his prognosis without surgery is not known except in a general way. In almost all instances the procedures are only palliative, a fact that must be weighed in the decision for surgery in borderline risks and particularly in patients with liver cirrhosis. It is also only fair to say that the successfully performed shunt operation leaves the patient with varices which, although less likely to bleed, are still a hazard; hemorrhage may and does occur after shunt procedures. Unfortunately the varices do not disappear after portal decompression. These are not arguments against operation but factors to be considered in each patient's situation. The shortcomings found in assessing the value of portacaval shunts are quite evident. At present there is no way of measuring pressure in the esophageal varices nor any method of determining portal pressure except at the time of celiotomy. Preoperative portal pressure in the intact subject cannot be measured. Factual evidence of the permanency of portal pressure reduction after shunt operations is not available. It is presumed that the majority of these shunts stay open but it is impossible to detect thrombosis in them. Whether or not we shall be assured in five or ten years that the patient with cirrhosis of the liver, hypertension, and varices can be substantially benefited by these procedures remains to be seen. For the moment the operations are sufficiently hopeful to warrant further trial. Clinical data presented by Blakemore on his operated patients is most encouraging. Concurrent with surgery all patients receive better medical therapy for liver disease all of which will tend to effect better results from surgery in terms of life extension in the patient. Since shunting of the portal blood into the caval system and reducing portal pressure seems to have no influence in causing a disappearance of esophageal varices as far as can be judged roentgenologically, it might be reasonable to propose that some attempt be made to eradicate varices after a shunt operation has been performed. The reduction in pressure in these varices alone is not an entirely satisfying accomplishment. As far as we know the combination of a preliminary shunt operation followed by injection of varices or esophagogastrectomy has not been done as yet. Few patients might be selected to undergo two procedures of such magnitude, yet, in the exceptionally good risk individual they might be done. The injection of esophageal varices after portacaval shunts have been performed is more feasible and perhaps should be attempted in all cases. There is evidence that in the next ten years a larger number of patients with portal hypertension the result of liver disease will present themselves because of the high incidence of hepatitis sustained by military personnel during World War II. The surgery of portal hypertension must be continued and every reasonable new idea tried out since the problem is not yet solved.

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Discussion

Dr. Robert R. Linton (Brookline, Mass.):—There is little I can add to the subject of portal hypertension and its treatment other than what Dr. Welch has so ably given us, except perhaps to give you some of our experiences at the Massachusetts General Hospital, and, if I may take the liberty of repeating some of the things Dr. Welch has already said, I would like to do so, chiefly to emphasize them.

In the statistics that Dr. Welch has already mentioned in reference to mortality rate from esophageal varices, obtained at the Massachusetts General Hospital by Dr. Shull from 1944 to 1945, I should like especially to draw your attention to the patients with cirrhosis of the liver. At the end of one year the mortality rate from this disease is about 50 per cent. Not all of these patients have died directly from esophageal bleeding, but the majority did or the hemorrhage was a contributing factor. From the statistics it is obviously a lethal disease so that if there is anything we can do to prevent bleeding from esophageal varices, it is worth-while.

The mortality rate in the so-called Banti's syndrome is much less, as it is a relatively young age group, and occurs in patients with normal livers.

The statistics serve to re-emphasize the seriousness of the condition. In 131 patients with portal hypertension, 99 of them died in the eleven-year period; 46

of them, or 46 per cent, died of hemorrhage; 90 of the deaths were cirrhotics and 41, or 45 per cent of them, died from hemorrhage alone.

I agree with Dr. Welch that the end-to-side splenorenal type of shunt is the preferable one, and these are my reasons for it. It is a partial shunt to the liver. The liver is not bypassed completely. Whether a patient with complete shunt remains in good nutritional balance is still something that has not been determined, so for that reason we feel if we can shunt the blood by some other means than the direct portacaval, it is advisable. I think there is another advantage to it, also, and that is, if you make a complete shunt of the portal bed by making a direct portacaval anastomosis, it may reduce the portal pressure so greatly that the speed of blood flow will be greatly reduced at the site of anastomosis, and thrombosis will occur.

I know of several cases in which portacaval shunts have been done and at autopsy were found to be thrombosed, and I have wondered if this might not be the reason. So far as I know, none of the splenorenal anastomoses that I have performed have thrombosed.

The emergency treatment of bleeding from the esophageal varices is a subject worth discussing for a moment. I was called on the telephone the other night from Washington, D. C., because a patient in one of the hospitals was bleeding from esophageal varices and was obviously going to bleed to death unless something was done. I was asked what could be done.

I believe the most satisfactory procedure is the placing of a balloon tube in the stomach and inflating it, and then drawing on the tube to impinge the balloon against the cardia of the stomach as first described by Rowntree. This procedure has saved the life of a number of our patients, and I am sure it is a very valuable emergency means of stopping bleeding from the esophageal varices.

We use a double-lumen tube, a simple, ordinary Miller-Abbott tube. The end of it has been cut off, and the balloon placed at a higher level than normally you would find. The balloon is connected with one of the lumens and the other lumen connects with the holes on the distal end of the tube, and in this manner you can make sure whether the patient is bleeding or not, because the stomach can be washed out and if he is not bleeding from his esophagus, you know you have the bleeding under control.

We have usually used a three-pound weight on the end of the tube in order to keep it "snugged up" against the cardia.

Another important method of treating a bleeding esophageal varices case that does not stop spontaneously, is by means of splenic artery interruption. This is an operation which has been described, and Dr. Welch has mentioned, as a definitive procedure. I prefer to use it only as a first-stage procedure preparatory to doing a shunt operation, and I have done this in a number of patients, with immediate cessation of bleeding, and the patients have improved.

One individual whose hemoglobin we couldn't get above 8 grams and a half, with daily transfusions, as soon as we tied the splenic artery, stopped bleeding

and his hemoglobin rose to 12 grams within a few days, so it may be a good operation as a first-stage procedure, preparing the patient for splenectomy and splenorenal anastomosis or, if you prefer, for direct portacaval anastomosis. Unfortunately it does not stop the bleeding in all cases.

Now, what are our results at the Massachusetts General Hospital? The first two years the mortality was very high. In 1947 it improved. In the large series in 1948 it really looked very encouraging, with twenty cases and only two deaths, a mortality of 10 per cent, which certainly is far better than if you leave the patients alone. For some reason or other we haven't seen so many cases in 1949. There have been two deaths in this year, so we have a total of 44 patients operated upon and nine deaths, with a 20 per cent mortality rate.

Next, what has happened to patients in whom we have done satisfactory shunts? We have a total of 25 cases operated upon up to July 1949. In three cases postshunt bleeding has occurred but in the other 22, none has been observed, which I believe speaks well for the procedure. A further and longer follow-up is of course necessary to truly evaluate the operation.

Then, the final point I should like to make is: Don't accept a patient with ascites alone for this operation, and even with ascites and esophageal varices, I think you want to approach the question of operation with considerable doubt, because my experience has been that patients with marked ascites, even with esophageal varices, are very poor operative risks.

Finally, if you, as a surgeon, have to do a splenectomy, or decide to do a splenectomy, for portal hypertension, I would please ask you to be prepared to do a splenorenal anastomosis at the same time, because, especially in the Banti's group, this may be the only chance you ever will have to do a satisfactory shunt.

Dr. George Miller (Boston, Mass.):—After Dr. Welch's fine paper and Dr. Linton's excellent discussion, there is very little left for me to say; however, there have been two points about this problem that have interested me for some time and one of those concerns the liver function. There has been a great deal of discussion about whether or not the shunt operations actually can improve the liver function as measured by the tests which we have available at the present time. It would seem that perhaps a great number of cases will need to be done before we can draw any conclusions in this regard.

It would seem to me that if we can prove that the liver function can be substantially improved in a good number of these cases, then we will be a little bit more encouraged about offering what is a fairly formidable procedure to patients who are very poor risks and, as is well known, it would seem to be true that the patients who are the poorest risks theoretically are to be benefited most by the operation.

Again, I was interested in another concept about which I first heard Dr. Welch speak, and which is perhaps only in the realm of possibility at the moment. That is that it is known that even after shunt operations, bleeding can occur from

the varices which may still remain, and if perhaps the liver function can be improved by some of these shunt operations and these patients survive for a reasonable length of time, it might then be reasonable to offer these patients some other type of therapy to get rid of the varices, such as the sclerosis, as done by Moersch, at the Mayo Clinic, or perhaps, which is a little more formidable, to subject them to a high resection.

Dr. C. Stuart Welch (Boston, Mass.):—I have enjoyed the discussion of this subject of portal hypertension by Doctors Linton and Miller. In regard to Dr. Miller's question of whether or not some direct attack on the varices should be made after portacaval shunts have been performed, I can only say that I have done no work in this direction. It does seem reasonable, however, that since varices are still present that attempts to obliterate them by injection could be carried out. This would require the collaboration of a skillful endoscopist. A more radical approach to the elimination of the varices after splenorenal anastomosis would be to perform a transthoracic esophagogastrectomy as recommended by Phemister or an almost complete abdominal gastrectomy as suggested by Wangensteen. In general, however, patients have done so well after portacaval shunts that it has seemed unwise to subject them to operations of this magnitude.

The question of whether or not portacaval shunts in themselves help to improve liver function in these patients has been brought up. On theoretical grounds it would seem that the shunt in itself could have no beneficial effect on the liver. It is perhaps better medical therapy which these patients obtain and follow subsequent to surgery together with the relief of their portal hypertension which has resulted in improved liver function in many cases. It has been postulated that diversion of the portal blood away from the liver may in fact be harmful. While it is possible that this may be true in the subject with a normal liver, portacaval shunts apparently have no ill effects in patients with cirrhosis of the liver or in other extrahepatic blocks. It is probable that in most cases very little blood is reaching the liver by the portal system in any event and that the blood supply of the liver is almost entirely via the hepatic artery.

THE EFFECT OF RESECTION OF THE SYMPATHETIC AND PARASYMPATHETIC INNERVATION OF THE STOMACH UPON GASTRIC ACIDITY*†

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A relatively small number of carefully studied cases has afforded opportunity for a further appraisal of the influence of the autonomic nervous system upon the secretion of hydrochloric acid by the stomach, as well as the modifications resulting from varying degrees of gastric resection. This has been a clinical study, with emphasis on the actual free acidity of the gastric juice under various circumstances, rather than a physiological study including exclusion of neutralizing diluents such as saliva or reflux enteric contents. In spite of the complexity of the factors operating, there has been a surprising statistical agreement in hydrochloric acid values and gastric juice volume following repeat studies on the same patient under similar conditions. To the degree that the operation is anatomically complete, it is possible to assess separately the effect of interruption of the sympathetic or parasympathetic nervous systems. Although gastroenterostomy lowers acidity in its own right, the postoperative free hydrochloric acid values following section of the vagus nerves alone or combined with gastroenterostomy have been sufficiently close that we have considered these two procedures as a group. We believe that resection probably alters the autonomic nerve supply to residual gastric tissue, thus variably clouding the demonstrable effect of gastrectomy. In addition, there is the complicating effect of regurgitation of duodenal contents. Nevertheless, we believe that by using a series of available tests, we can gain information about the factors controlling the levels of free hydrochloric acid in the gastric juice of ulcer patients, and by means of the same tests determine the effect of removing these factors, singly or in combination.

Method of Study

We have used a series of four tests before and after surgery in each case, as far as practicable. They included the fasting basal, insulin, broth and histamine tests to measure physiologic neurogenic[1], potent neurogenic[2,3,4], physiologic chemical[5], and potent chemical[4] effects respectively. All secretory specimens were collected by constant suction, with careful attention to insure minimal loss of gastric juice through tube stoppage. Wolf and Wolff[6] have shown that mechanical stimulation of gastric mucosa by moderately vigorous massage with a glass tube has essentially no effect upon gastric acidity, and a fleeting effect upon motility. The stimulation provided by the presence of the Levin tube in the stomach

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throughout these studies has been a constant. Table I demonstrates the average peak free hydrochloric acid values obtained during these tests in a series of patients with duodenal ulcer, hypertension with and without duodenal ulcer, gastric ulcer, and normal gastrointestinal tracts. As is generally known, there was wide scatter of values in each category, with a good deal of overlap between divisions. Nevertheless, this small series arranged itself with generally higher acid values for the duodenal ulcer group than for those patients with gastric ulcer, while the hypertensives, both with and without ulcer, were generally high also. This brings out the point made by Bloomfield and French[7], that some patients may have ulcer with high or low acid, while high acid, as in the hypertensive group, is not invariably accompanied by ulcer. It is clear, therefore, that a critical level of acidity probably exists, beyond which peptic ulceration occurs, and that this level varies with the particular patient. In the absence of a specific method for determining the critical level of acidity in a given patient, one is obligated to reduce acidity sufficiently to offer reasonable safety from recurrence. There is no

TABLE I

AVERAGE PEAK FREE HCl VALUES (TEN MINUTE SAMPLES) IN CLINICAL UNITS

Category	No. Cases	Basal	No. Cases	Insulin	No. Cases	Broth	No. Cases	Histamine
Duodenal Ulcer	83	52	76	93	78	74	76	100
Hypertension with Duodenal Ulcer	22	41	20	95	20	69	19	103
Hypertension	8	48	8	100	8	82	8	111
Gastric Ulcer	22	25	21	81	22	63	20	93
Normals	6	13	4	85	6	55	5	85

doubt that achlorhydria to histamine stimulation offers great assurance that acidity is below the critical level. On the other hand, we wonder whether achlorhydria to physiologic stimuli, such as broth, might not in time prove as adequate a guide to the modification of acidity below the hypothetical critical level, as the more potent stimulus of histamine. The corollary is that we have come to look upon achlorhydria to the fasting basal and broth tests as potentially important criteria in determining probable protection from further ulceration postoperatively, while the insulin test demonstrates mainly the completeness of section of the vagus nerves. We have retained the histamine test primarily for completeness in forming a basis for comparison with other data. Repeated fasting basal tests were substituted for night secretions, following our impression, confirmed statistically in 23 cases, that both tests were measuring the same gastric function. There was complete agreement in maximal HCl values, while volume was slightly but consistently higher during the basal as compared with the night secretion in respect to volume per unit time. Statistical analysis of basal tests repeated one day to several weeks apart under similar conditions in the same patient, showed un-

doubted comparative statistical validity in 108 cases with regard to volume, average free hydrochloric acid per hour, and peak ten-minute free hydrochloric acid concentration, although rare deviations were noted. The routine of the tests was as follows. After clear fluid for supper, and nothing by mouth during the night, a Levin tube was passed through the nose into the stomach in the morning. When the patient appeared calm, adjusted to the tube, and secretions were coming steadily, specimens were collected under constant suction at ten minute intervals for one hour. The insulin test followed, and secretions were collected at half-hour intervals for three hours following the administraton of 15 units of insulin intravenously. Blood was withdrawn for sugar determinations prior to and at three half-hour intervals following insulin. On another day, following similar preparation, the fasting basal test was repeated. Then 80 cc. of peptone-beef broth was instilled through the tube into the stomach, care being taken not to suggest that the liquid was a food. This was left in place twenty minutes and the residue withdrawn. Secretions were again collected under constant suction at ten minute

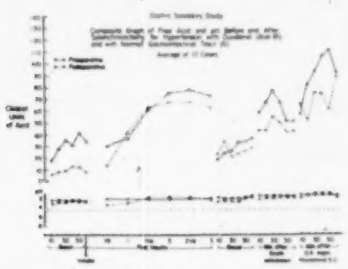

Fig. 1

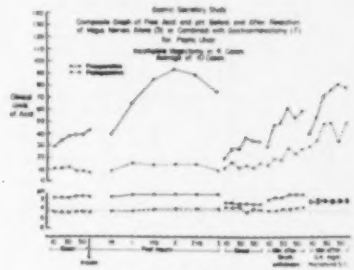

Fig. 2

intervals for one hour. Finally, the patient was given 2 cc. of histamine acid phosphate (0.4 mg. histamine) subcutaneously, and secretions were again taken at ten minute intervals for one hour.

Volume was measured directly. Free hydrochloric acid was determined by titration against 0.1 N NaOH, with Topfer's solution as indicator, using the canary-yellow color as end-point at approximately pH 3.0. A constant flow calomel-glass electrode pH meter permitted immediate determination of hydrogen ion concentration as the gastric juice left the stomach. We have selected pH 4.5 as the critical level, above which negligible pepsin digestion ocurs. Hydrochloric acid is recorded in clinical units, and each unit is equal to one milliequivalent of HCl. Total milliequivalents per hour were calculated from the average free HCl per hour multiplied by the hour volume of gastric juice divided by one thousand. While this computation proved statistically valid in repeat tests, such was not true of peak gastric activity measured by maximal milliequivalents of free HCl per ten minutes during a given test, where approximately fifty per cent of 66 repeat peak figures differed from the primary figures by large amounts. Since the average hour free hydrochloric acid concentration, the peak ten minute free hydrochloric acid

TABLE II

AVERAGE PEAK FREE HCl VALUES (TEN MINUTE SAMPLES) AND AVERAGE HOUR FREE HCl VALUES BEFORE AND AFTER VARIOUS SURGICAL MANEUVERS

Operation	No. Cases		Basal		Insulin		Broth		Histamine		Per cent* Achlor.
			Peak	Aver.	Peak	Aver.	Peak	Aver.	Peak	Aver.	
Autonomic Nervous System											
Splanchnicectomy	12	Pre	45	28	91	61	80	63	118	86	
		Post	32	14	87	57	66	39	97	59	0
Vagectomy with or without PGE	10	Pre	69	52	106	79	76	52	93	71	
		Post	16	12	23	13	49	34	62	46	10%
Splanchnicectomy with Vagectomy	5	Pre	52	35	98	67	79	55	102	74	
		Post	16	8	27	15	61	48	66	53	0
Gastric Resection											
50% Gastric Resection	4	Pre	43	32	39	23	62	48	82	57	
		Post	6	4	19	9	8	4	28	18	25%
2/3 - 4/5 Gastric Resection	9	Pre	38	24	63	43	53	39	95	73	
		Post	8	3	20	16	14	6	36	18	30%
3/4 - 4/5 Gastric Resection	7	Pre	41	27	72	51	53	40	102	75	
		Post	8	3	17	9	13	4	31	13	43%
Combinations											
Splanchnicectomy and Antral Resection	4	Pre	62	44	97	67	78	60	99	81	
		Post	17	10	35	14	10	6	51	33	50%
50% Gastric Resection with Vagectomy	12	Pre	58	35	102	71	86	66	99	77	
		Post	5	1	5	3	2	1	28	15	67%
4/5 Gastric Resection with Vagectomy (Before and After Resection of Vagus Nerves)	1	Pre	0	0	22	21	13	10	26	18	
		Post	0	0	0	0	0	0	35	9	100%
	1	Pre	40	23	72	54	60	36	82	43	
		Post	0	0	0	0	0	0	38	22	

* Achlorhydric to Basal, Insulin and Broth Tests.

TABLE III

AVERAGE TOTAL MILLIEQUIVALENTS FREE HCl PER HOUR BEFORE AND AFTER VARIOUS SURGICAL MANEUVERS

Operation	No. Cases		Basal	Per cent Reduct.	Insulin	Per cent Reduct.	Broth	Per cent Reduct.	Histamine	Per cent Reduct.
					Autonomic Nervous System					
Splanchnicectomy	12	Pre	1.94		5.43		6.06		14.33	
		Post	0.63	68%	6.46	+20%	4.05	33%	8.09	44%
Vagectomy with or without PGE*	10	Pre	4.55		13.30		4.27		16.08	
		Post	1.66	63%	1.27	90%	3.19	25%	8.69	46%
Splanchnicectomy with Vagectomy	5	Pre	3.31		5.08		4.01		7.50	
		Post	0.50	85%	0.19	96%	3.05	25%	4.23	43%
					Gastric Resection					
50% Gastric Resection	4	Pre	2.90		1.33		5.05		7.59	
		Post	0.25	91%	0.29	78%	0.21	96%	1.37	82%
2/3 - 4/5 Gastric Resection	9	Pre	2.83		4.97		4.85		11.96	
		Post	0.22	92%	0.84	83%	0.41	92%	1.63	86%
3/4 - 4/5 Gastric Resection	7	Pre	3.34		5.80		5.78		21.18	
		Post	0.21	94%	0.89	85%	0.29	95%	1.18	94%
					Combinations					
Splanchnicectomy and Antral Resection	4	Pre	4.75		9.97		6.15		20.37	
		Post	0.38	92%	1.98	80%	0.22	96%	4.95	76%
50% Gastric Resection with Vagectomy **	12	Pre	4.30		9.86		9.73		18.94	
		Post	0.15	97%	0.11	99%	0.04	99%	1.17	94%
4/5 Gastric Resection with Vagectomy (Before and After Resection of Vagus Nerves)	1	Pre	0		0.48		0.77		0.66	
		Post	0	100%	0	100%	0	100%	0.57	14%
	1	Pre	2.55		9.77		4.68		9.20	
		Post	0	100%	0	100%	0	100%	4.27	54%

*3 incomplete vagectomies
**2 incomplete vagectomies

levels, and the total milliequivalents of free hydrochloric acid are statistically valid figures, we have used them as a basis for the comparison of the effects of various procedures upon the gastric acidity.

Results

1. *Splanchnicectomy*:—Twelve patients, 6 of whom had duodenal ulcer, the remainder with apparently normal gastrointestinal tracts, had splanchnicectomy for hypertension. Because both sets of figures were so similar, both classes of patients are considered as a group. Figure 1 is a composite graph of free HCl and pH in the twelve patients. It may be noted that a slight, but definite lowering of acid values resulted following each test, with some overlap during one set of basals, and during the insulin tests. In Table II may be seen that all peak ten minute free HCl and average hour free HCl values have been lowered, without the appearance of achlorhydria to any test. However, in Table III may be found that all total hour milliequivalents also fell following splanchnicectomy, except in the case of the insulin stimulation, where sufficient increase in volume output occurred to compensate for the slight lowering of acid concentration, with the

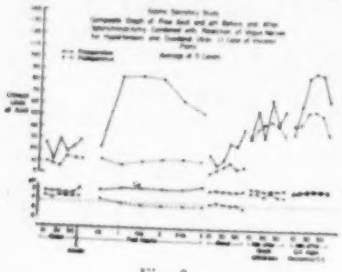

Fig. 3

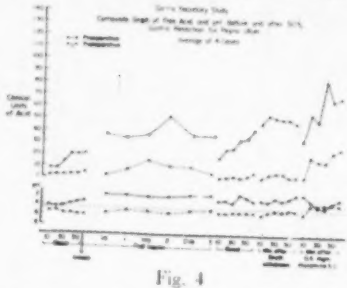

Fig. 4

result that total hour milliequivalents of free HCl were increased from 5.43 meq. to 6.46 meq. as an average. As will be mentioned later, this is the only evidence for a possible release of the vagus mechanism following ablation of the sympathetic pathways, and seems to occur only on potent stimulation of the vagus nerve. No striking change in pH occurred.

2. *Vagectomy with and without gastroenterostomy*:—Ten patients comprised this group, and because of the presence or threat of obstruction, only three had simple section of the vagus nerves. Four of the cases were adjudged to have had incomplete anatomic section of the vagus nerves, as indicated by a relatively heightened response to insulin compared with the fasting basal studies postoperatively. Figure 2, a composite graph of these cases, shows the definite lowering of free HCl to all tests, most marked following insulin, and moderate in the basal studies, but occurring also following the chemical stimulations of broth and histamine. The pH was raised to the region of the critical level (pH 4.5) postoperatively during all tests except histamine. However, Table II shows that all peak and average free HCl values were lowered, including those following hista-

mine, but this effect was more marked during the neurogenic studies of fasting basal and insulin tests. The total milliequivalent figures in Table III demonstrate well the striking postoperative fall of total free acid following insulin, from 13.30 meq. to 1.27 meq. per hour. The basal test is also lowered more than either broth or histamine, although a definite change from 16.08 meq. to 8.69 meq. may be seen in the histamine test. Only one patient, comprising 10 per cent of the group, achieved postoperative achlorhydria to the basal, insulin and broth tests, while none were achlorhydric to histamine.

3. *Splanchnicectomy combined with vagectomy*:—Four patients had splanchnicectomy combined with resection of the vagus nerves for hypertension and duodenal ulcer, while a fifth had combined procedures for persistent visceral pain. Figure 3 is a composite graph of free HCl and pH in the five cases. Again the predominant effect is a lowering of the free HCl values during the neurogenic tests, basal and insulin, with a less marked effect during chemical stimulation, broth and histamine. It may be noted that removal of both branches of the autonomic nervous system did not completely abolish gastric hydrochloric acid production during fasting basal activity, denoting a small component of chemical activity in this response under some conditions.

Compared with Figures 1 and 2, it may be seen that the combined sympathetic-parasympathetic procedure produces an effect not dissimilar from that following vagectomy alone, both with regard to free HCl and pH. This is also apparent in Table II, where magnitude of change in peak and average free HCl during each test before and after operation is quite similar for the vagectomy and combined vagectomy-splanchnicectomy group. Although the primary insulin and histamine values in Table III are roughly twice as high in the vagectomy group compared with the combined group, the percentage reduction in total milliequivalents of free HCl per hour following each test is of the same order for both groups. It should be noted that although the reduction in average free hydrochloric acid values was of the same degree in the vagectomy and splanchnicectomy-vagectomy groups, there was a sufficient increased reduction in volume during the basal tests of the combined group to reduce its total acid output per hour 85 per cent in contrast to the reduction of 63 per cent in average total milliequivalents of free hydrochloric acid for the vagectomy group. Similarly, the percentage reduction of the combined group following insulin stimulation, 96 per cent, is slightly greater than the reduction for the vagectomy group, 90 per cent, from the aspect of total free acid output. Thus only in the total free acid output per unit time following neurogenic studies is there evidence for a slightly greater effect following interference with both divisions of the autonomic nervous system, in contrast with resection of the vagus nerves alone, and this effect is achieved through reduction in volume of gastric juice. Achlorhydria to any test was not achieved in this group.

4. *Fifty per cent gastric resection*:—Because of the generally low HCl values obtained to both neurogenic and chemical stimuli in four patients, two with

gastric and two with duodenal ulcers, a partial gastric resection was performed. In Figure 4, a composite graph of the free HCl and pH values in the 4 cases, it may be seen that this operation was sufficient to effect a reduction of the relatively low preoperative HCl values to very low levels following all tests except the histamine. One case became achlorhydric to the basal, insulin and broth tests. Postoperative pH rose above the critical pH 4.5 level in the basal, insulin, and broth tests, but was essentially unchanged following histamine stimulation, in spite of a lowering of the corresponding free HCl values. In Table II it may be seen that the greatest percentage reduction of both peak and average free HCl occurred in the broth test, consistent with Edkin's hypothesis[8] that the antrum is primarily concerned in physiologic chemical stimulation of gastric HCl. Table III also shows a general shift of total milliequivalents of free HCl per hour to low levels, most marked in the broth test. If histamine stimulates the parietal cells directly, and only 50 per cent of the stomach has been resected, the fall from 7.59 meq. to 1.37 meq. following histamine stimulation is difficult to explain.

Two-thirds to four-fifths gastric resection:—Nine patients, 7 with gastric ulcer, and 2 with duodenal, had subtotal gastric resection alone. Because of the variation of weight of resected specimens to the probable weight of the stomach, as well as the variation in the surgeon's estimate of percentage stomach removed, we have chosen to group these cases generally as comprising 2/3 - 4/5 resection. Figure 5 is a composite graph of the free hydrochloric acid and pH values before and after this maneuver. Again a general reduction in free HCl is in evidence, least marked in respect to histamine, while the pH ranges about the critical level of 4.5 postoperatively except following histamine and insulin stimulation. In comparison with 50 per cent gastric resection in Table II, it may be seen that the changes in peak and average free hydrochloric acid values following each test are essentially the same for both the 50 per cent and 2/3 - 4/5 resection groups. This same relationship holds in Table III, where it may be seen that the total free acid is similarly affected, although it may be noted that a larger reduction appears to be effected following broth stimulation by the 50 per cent resection than by the larger gastrectomy. This apparent effect probably depends on the errors inherent in the method, and undoubtedly represents variations of the same general order. Similarly, the slightly increased reductions following the larger gastrectomy in comparison with the smaller, of 83 per cent against 78 per cent for the insulin tests, and 86 per cent against 82 per cent for the histamine stimuli, are probably close enough to be regarded as changes of essentially similar magnitude. This suggests that beyond the removal of the antrum, further increments in resection of parietal cellbearing tissue have relatively smaller effects in reduction of gastric free hydrochloric acid. Achlorhydria to the basal, insulin, and broth tests appeared in three of the cases, 30 per cent, while one of these cases was totally achlorhydric.

Three-quarters to four-fifths gastric resection:—For purposes of comparison, 7 cases with at least 3/4 and possibly 4/5 gastric resection are presented, of which

5 had gastric and 2 duodenal ulcers. Figure 6, the composite graph of free hydrochloric acid and pH values for this group, does not differ markedly from Figure 5, representing the smaller resection. The comparable changes in peak free hydrochloric acid, and average free hydrochloric acid for the 2/3 - 4/5 and 3/4 - 4/5 groups, as recorded in Table II, show similar changes, except for a slight trend towards increased reduction in values following insulin and histamine for the larger resection. This would suggest that the physiologic functions of the stomach as measured by the basal and broth tests are less affected than those measured by the potent stimuli of insulin and histamine, as resections increase beyond two-thirds of the stomach. In Table III it appears that the effect on total free acid is mainly following histamine, where in comparison of the 2/3 - 4/5 with the 3/4 - 4/5 resection, the percentage reduction of total free acid increases from 86 per cent to 94 per cent. This would be in keeping with the postulate that histamine stimulates parietal cells directly, more of which have theoretically been removed in the larger gastrectomy, but probably actually represents changes of the same order. Achlorhydria to the basal, insulin and broth tests appeared in three cases, or 43 per cent.

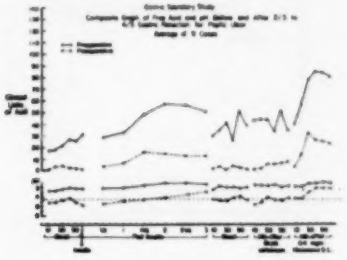

Fig. 5

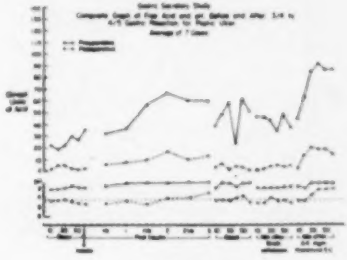

Fig. 6

5. *Splanchnicectomy combined with antral resection*:—Five patients have had splanchnicectomy combined with gastric antral resection, but data are available only on four. The first two patients with known duodenal ulcer had splanchnicectomy, one for hypertension, and one for the relief of visceral pain following cholecystectomy. When these patients later required surgery for the control of hemorrhage, the first portion of the duodenum was excised, the bleeding vessel ligated, and the ulcer crater exteriorized. In addition a limited gastric resection was performed. It was estimated that not more than one-third of the stomach was resected in each of these cases. A surprising achlorhydria was noted in the studies following this fortuitous combination of operations. However, there were no preoperative data on these patients, and the routine of tests which we ordinarily used was only partially carried out after operation. Therefore, when the third patient, who had fortunately had complete secretory studies before and after splanchnicectomy, presented the same problem of hemorrhage, limited gastric resection was selected as the operation of choice. Only the antrum was removed with a small cuff of parietal cell-bearing tissue, as proven by microscopic

study. The specimen weighed 105 grams. Virtual achlorhydria again resulted as may be seen from Figure 7, a graph of free HCl values before and after operation in this patient. Two further cases of duodenal ulcer were then treated by combined splanchnicectomy and antral resection. Postoperatively there was marked reduction of HCl to all tests in these two patients, but achlorhydria did not appear, except in response to broth stimulation in one patient. In Figure 8 may be seen the general response to this combined procedure, in a composite chart prepared from the available data on four of the patients. There is a lowering of free HCl following all tests, most marked in the basal, insulin, and broth responses. In Table II it may be noted that the addition of splanchnicectomy to a smaller gastric operation than the 50 per cent resection produces a definite lowering of all acid values, but only in the insulin test does this combination produce a greater percentage reduction in HCl values than the 50 per cent resection alone. The reason for this discrepancy may be apparent in Table III, where the relatively higher preoperative total milliequivalents of free HCl during the insulin test will be noted in the splanchnicectomy-antral group contrasted with the 50 per cent gastric resec-

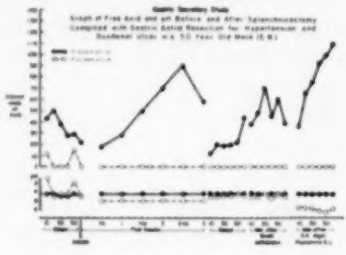

Fig. 7

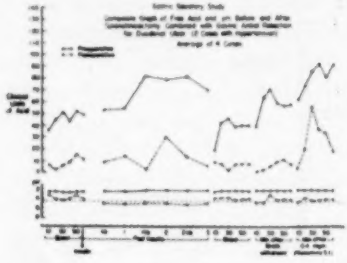

Fig. 8

tion, 9.97 meq. against 1.33 meq. on the average. A similarly higher preoperative histamine may also be seen in the same table. The combined operation failed to raise the pH to the degree achieved by the 50 per cent gastric resection, as a comparison of Figures 4 and 8 will show.

6. *Fifty per cent gastric resection with vagectomy*:—Twelve patients, one with gastric ulcer, one with gastric and duodenal ulcers, and the remainder with duodenal ulcers, were treated by partial gastric resection and section of the vagus nerves. Figure 9 demonstrates, in a composite graph for the group, the reduction in the usually high preoperative free HCl values to almost achlorhydria except in the response to histamine. Achlorhydria to the basal, insulin, and broth tests was achieved in 8 cases, 67 per cent, and the values of the other 4 cases to these tests postoperatively were consistently low. Except following histamine, the postoperative pH values were well above the critical level of pH 4.5. The generally low postoperative peak and average free HCl values in the basal, insulin and broth tests may be seen in Table II. A similar fall in total milliequivalents of free HCl is present in Table III, where a striking fall to histamine as well, may be observed.

On the basis of a comparison of postoperative basal and insulin responses, two of these cases were considered to have had incomplete section of the vagus nerves.

7. *Four-fifths gastric resection with vagectomy*:—An example is presented of a 60 year old male (D.S.) with a jejunal ulcer five years following a 4/5 gastric resection for duodenal ulcer. His peak free HCl values, as may be seen in Table II, were 22 units to insulin, 13 units to broth, and 26 units to histamine stimulation. He was achlorhydric during the fasting basal test. Section of the vagus nerves was performed after which he became achlorhydric to all tests except histamine. The data graphed in Figure 10 demonstrate the relatively low acid values which may accompany a jejunal ulcer, while postoperatively the ulcer disappeared following establishment of achlorhydria to the basal, insulin and broth tests, but not to histamine. The definite shift of the pH towards the neutral is also evident. We have another parallel case in our experience, J. K., a 49 year old male, with jejunal ulcer 1½ years following 4/5 gastric resection. His acid values preoperatively were moderately high. Transthoracic section of the vagus nerves was followed by achlorhydria to basal, insulin, and broth tests as evidenced in Figure 11,

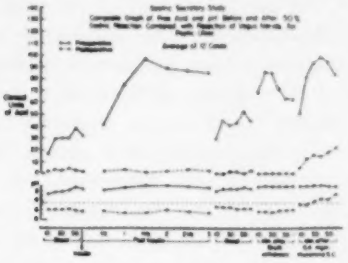

Fig. 9

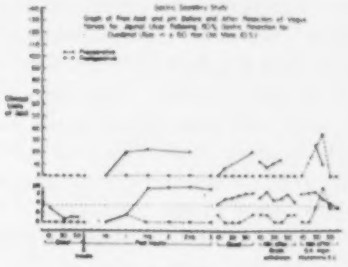

Fig. 10

where the shift of pH towards neutral is again evident. In spite of the persistent response to histamine, the jejunal ulcer disappeared.

Comment

The factors influencing the secretion of HCl by the stomach may be grouped into two general categories, neurogenic and chemical. Because the HCl production is so obviously important in the causation of peptic ulcer, and its control, the keystone of medical and surgical therapy of ulcer, we have been interested in the variations of neurogenic and chemical factors active in maintaining HCl levels in ulcer patients, and in the manner in which these factors are modified by surgery. We have noted for some time, and agree with Griswold[9], that some ulcer patients appear to have highly active neurogenic, others highly active chemical, still others both highly active neurogenic and chemical factors, while a fourth group of patients seem to activate ulcers with rather low activity of both these factors. It would seem that the most active neurogenic influence is relayed over the vagus nerve, as the abundant evidence attests since Dragstedt[10,11] reintroduced section of these nerves. On the other hand there has been a role, not yet clearly defined,

played by the sympathetic nerves in the control of HCl, and we have been fortunate to have had the opportunity to collect some evidence concerning this problem. The major chemical control of HCl production has long been linked with the antrum, since Edkins[8] first demonstrated the effect of its extract in 1906. The other factors which influence HCl production, such as mechanical stimulation, gastric secretagogues, intestinal hormones, variations in blood CO_2 and anemia, are probably not of constant importance in the regulation of gastric HCl in the ulcer diathesis, except that the intestinal hormones may play a role in the prevention of anastomotic ulcer as shown by Wangensteen[12]. Our interest has therefore been directed towards further understanding of the relative roles of the sympathetic and parasympathetic nervous systems, and the influence of the antrum in gastric HCl regulation, as well as any possible interrelationship between these three factors.

The major portion of the data on the activities of the sympathetic and parasympathetic nervous systems in the gastrointestinal tract have dealt with motility. Although anatomically and physiologically both systems have been shown to have mixed components and overlap of function[13], the earlier concept of essential antagonism proposed by Hess[14], and clarified by Cannon[15], has apparently been brought from the field of motor function where it was propagated, and applied to gastric secretory activity. Thus both Weeks[16] et al, reporting perforation of a duodenal ulcer following transthoracic section of the vagus nerves combined with splanchnicectomy, and Blegen et al[17], reporting aggravation of a gastric ulcer shortly after splanchnicectomy, suggest imbalance of this antagonism as the causative factor in the activation of the ulcers. Experimentally, Baxter[18] found slight increase in volume, slight increase in free acid, no change in total acid, and a slight increase in digestive activity following splanchnic stimulation in dogs, while repetitive stimulation in fistula dogs produced an alkaline juice rich in mucin[19]. Heslop[20] found that splanchnicectomy in dogs in no way influenced the normal acidity of the gastric juice permanently. Hess and Faltitschek[21] reported no essential change in acid levels immediately following 7th right dorsal paravertebral block done to relieve pain in thirteen patients. Von Gaza[22] had previously produced the same result in one patient by section of corresponding sympathetic rami, but did not report the gastric secretions. Baxter[18] quotes Pieri and Tanferna to the effect that these maneuvers diminish acidity in normals and in patients with gastric ulcer. Froehlich[23] reported 25 cases of unilateral and bilateral splanchnicectomy for gastroduodenal ulcer. At the four year follow-up period, 14 patients had no roentgenological evidence of ulcer and were symptom free, while 11 patients had had recurrence or primary failure. Blegen[17] cites failure of ulcer symptoms to improve permanently in 8 cases of unilateral or bilateral splanchnicectomy reported by Sicard. Moore[24], in the discussion following an ulcer symposium, stated that the acid values were low in young people with hypertension and without advanced organ change. In a few patients studied after splanchnicectomy he had noted that the insulin reaction was not abolished. With a shift of emphasis to the

state of the gastric mucosal circulation, de Sousa Pereira[25] found increased healing of wounds of the gastric mucosa in 16 dogs after unilateral splanchnicectomy, and in 1 dog after bilateral splanchnicectomy, in contrast to 13 control dogs similarly wounded but with all nerves intact. Carrying this work further, the same author noted roentgenological healing of gastric and duodenal ulcers with relief of symptoms in 17 out of 18 patients treated with repeated splanchnic blocks over periods varying from one to two months. He reported no secretory studies on these patients. The sum of this meagre information is that the splanchnic nerves may have slight control over HCl in dogs, and that splanchnicectomy may have no effect or diminish acidity in humans. The general impressions of authors such as Alvarez[13], Babkin[4], Dragstedt[26], and Kuntz[27] are against the view that the two branches of the autonomic nervous system act in an antagonistic manner on the gastric secretory mechanism. If mutual antagonism existed, one would expect removal of sympathetic influence to result in an increased secretion due to unrestrained vagal action.

In the present study, splanchnicectomy actually caused a reduction in basal secretion, both with respect to concentration and total amount of acid. The secre-

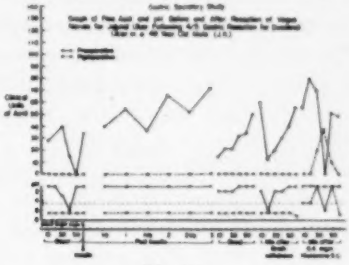

Fig. 11

tion was also diminished following the broth and histamine stimuli. Although there are too few cases for statistical significance, it is suggestive that a slight increase in the total amount of acid occurred following vagal activity induced with insulin. Thus, there seems to be little evidence for striking secretory vagal preponderance postoperatively, and it is important to note the marked decrease in basal secretion. These are early postoperative results, but it seems unlikely that a later rise in gastric acidity to physiologic stimuli will ensue. Our later postoperative studies in progress seem to bear this out. If subsequent investigation demonstrates an increase in the ulcer diathesis following splanchnicectomy, it appears probable that some factor other than HCl will be found responsible.

The secretory results following vagectomy, with or without gastroenterostomy, are in agreement with the HCl values published by authors such as Dragstedt[28], Moore[29], Thornton[30], Walters[31], Meyer[32], Warren[33] et al. The preponderant effect of the vagus nerve is upon the neurogenic gastric activity, and this to a far greater degree than the change produced by the sympathetic nervous system. We have noted, as have Meyer[32] et al and Grimson[34] et al, that section of the vagus

nerves also lessens the chemical activity of the stomach. As may be seen in Tables II and III, the fall in average concentration of gastric free HCl, as well as the total amount of free acid, is of the same order in the broth and histamine tests following either splanchnicectomy or vagectomy, suggesting that both branches of the autonomic nervous system equally affect the chemical function of the gastric HCl regulatory mechanism.

As has been stated, the effect of combined splanchnicectomy-vagectomy is essentially that of vagectomy alone, including the lowering of the chemical responses. This makes it apparent that the vagus is the major neurogenic factor in gastric HCl secretion. But while each division of the autonomic nervous system equally lowers the chemical response, their dual withdrawal lowers that response only to the degree of a single ablation of one or the other autonomic divisions, suggesting a critical level of chemical activity independent of nervous potentiation.

Since Edkins[8] described the activity of antral extract in the chemical regulation of gastric secretion, the importance of this area has been emphasized by the failure of exclusion operations, as well as the reduction in acidity following antral resection or antral mucosal excision in staged operations[35]. Woodward[36] et al recently demonstrated the importance of the antrum in HCl secretion in Pavlov pouch dogs, where an average reduction of 84 per cent was effected in twenty-four hour HCl output following antrectomy. The marked reduction in HCl response following 50 per cent gastric resection, especially to the basal and broth tests, but also to the histamine, bear out this general experience. The failure of the insulin response to fall to the same degree as the other studies following 50 per cent gastric resection suggests that a larger proportion of this response is independent of antral action than the basal, broth or histamine studies. As larger amounts of stomach are resected, 2/3 to 4/5, little change occurs in the magnitude of reduction following basal or broth tests, but relatively larger changes occur in the insulin and especially the histamine reactions. This would make the antrum seem the center of the physiologic fasting basal and broth studies, while the more potent insulin and histamine stimuli react generally and are further limited by additional removal of parietal cell-bearing tissue. These abnormal stimuli, insulin and histamine, would seem relatively more independent of the presence of the antrum than the physiologic situations of fasting activity and broth stimulation.

The fact that the chemical HCl response seems to be potentiated by the sympathetic nervous system makes a combination of splanchnicectomy and antral resection seem logical in the control of gastric acidity. The earlier cases with achlorhydria made it appear that a definite synergism might exist between these factors. However, further experience, presented in Figure 8, suggests that the combined effect is mainly that of antral resection with respect to HCl regulation. The presence of conflicting reports cited[16,17,18,23,25] concerning the benefits of splanchnicectomy alone in the therapy of peptic ulcer might indicate that this maneuver influences one of the other factors included in the ulcer diathesis, such as the circulation, and its combination with other surgery such as antral resection,

might prove of value. Further investigation of these preliminary findings is being carried out clinically and in animals.

The fact that both neurogenic and chemical responses are influenced by the action of the intact vagus, makes the combination of vagectomy with antral removal a potent HCl lowering maneuver. This reasoning is the essence of the 50 per cent gastric resection and vagectomy group, where striking reduction of acid was effected to the basal, insulin and broth tests in all patients. Eight patients out of the 12 became achlorhydric to these tests. Our experience is in agreement with Colp's[37], who found the addition of vagectomy to subtotal gastrectomy to increase the percentage achlorhydria to neurogenic tests from 67 per cent to 95 per cent, and to increase the percentage achlorhydria following gruel chemical stimulation from 55 per cent to 100 per cent. In our series the addition of vagectomy to 50 per cent gastric resection increased the broth achlorhydria from 2 in 4 cases to 10 in 12 cases. Only 2 of our 7 cases of 3/4 - 4/5 gastric resection were achlorhydric to histamine, in comparison to the 67 per cent achlorhydria attained by Bartels[38] in 28 cases, or the 85 per cent achlorhydria to triple histamine stimulation found by Wangensteen in 173 cases, as reported by Gaviser[39].

As stated earlier, however, in measuring the chemical factor active in the ulcer patient, we wonder if the important criterion may not be the response to broth, because this stimulus more nearly approximates the normal chemical activity of a particular patient. It seems probable that stimulation to the degree effected by histamine injection rarely occurs during physiologic activity. If later statistical study should prove this hypothesis correct, it would provide the means for offering safety from recurrence with a lesser operative procedure than that presently accepted. Although we have been interested in what might constitute the minimal generally safe operation, we also feel that preoperative classification according to activity of physiologic neurogenic and chemical factors, might lead to greater discretion in the selection of the proper maneuver for the particular patient. The realization of such selection would do much, perhaps, to narrow the gap between the minimal procedure consistent with safety from recurrence, and the side effects attendant upon more extensive operative maneuvers. Part of such evaluation, of course, must await the clarification of the late effects on hydrochloric acid production of section of the vagus nerves. At the present time, we are favorably impressed by the physiologic effect of 50 per cent gastric resection combined with section of the vagus nerves. It has been the most dependable procedure for producing or closely approximating achlorhydria in patients having the greatest capacity for producing HCl. Only time will tell whether the striking achlorhydria or near-achlorhydria attained to the physiologic stimuli will correlate with freedom from ulcer recurrence in this group. Similarly, only later appraisal will determine whether possible side effects added by section of the vagus nerves will outweigh the benefits of less radical gastric resection in this combined operation. This study is in progress.

Conclusions

A small number of carefully studied cases have been used to assess the relationship of the sympathetic and parasympathetic nervous systems and the antral section of the stomach in the regulation of the HCl levels of gastric juice under clinical conditions. These are early postoperative results for the most part; later studies are in progress. While few of the groups contain statistically significant numbers, trends have been noted with obvious reservations. It has been found that to the extent that gastric HCl production is governed by neurogenic and chemical factors, four groups exist, comprising the possible combinations of preponderant activity of one or the other factor, marked action of both, or generally low activity. These studies were selected to demonstrate the effect of varied surgical maneuvers on each of these factors, but with the major emphasis on physiologic factors which might be assumed to operate during life, rather than on potent stimuli which probably only occur in the laboratory.

1. Splanchnicectomy does not augment free HCl levels, except that following insulin stimulation of the vagus, a sufficient increase in volume occurs to counteract a slight fall in acid concentration, resulting in a slight rise in total acid output per unit time.

2. Vagectomy markedly lowers HCl production following neurogenic stimulation, and moderately lowers acid levels following chemical stimulation. The fasting basal levels are markedly reduced.

3. Combination of splanchnicectomy with vagectomy produces essentially the effect of vagectomy alone on gastric free HCl levels.

4. Fifty per cent gastric resection lowers both neurogenic and chemical HCl levels postoperatively, with the smallest change occurring following insulin stimulation of the vagus.

5. Two-thirds to four-fifths gastric resection produces an effect similar to 50 per cent gastric resection on the physiologic studies, fasting basal and broth. Three-quarters to four-fifths gastric resection produces a comparable effect except that the effect on the potent stimuli of insulin and histamine is increased over the smaller resection group.

6. Splanchnicectomy combined with antral resection produces an effect similar to 50 per cent gastric resection on the whole, but holds some promise of beneficially modifying factors other than acidity active in the ulcer diathesis, such as circulation.

7. The addition of vagectomy to 50 per cent gastric resection results in a lowering of gastric free HCl values in all categories, including striking lowering of acid following the basal, insulin, and broth studies. Achlorhydria to these tests was achieved in 8 out of 12 patients. The pH during these tests was consistently above the critical level, pH 4.5, implying negligible peptic activity.

8. Two cases are presented demonstrating the occurrence of anastomotic ulcer following 4/5 gastric resection. In one the acid values were very low and in the

other quite high. The addition of vagectomy produced achlorhydria to the basal, insulin, and broth tests in both cases, and was followed by healing of the ulcers, although a small amount of HCl persisted in response to histamine stimulation.

9. It appears definite that the antral function depends in part on the intact autonomic nervous system. Removal of either parasympathetic or sympathetic pathways will lower the gastric response to chemical stimuli, roughly to the same degree. Ablation of both divisions of the autonomic nervous system lowers chemical response no more than section of either the vagus or splanchnic nerves alone.

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Discussion

Dr. John J. Byrne (Boston, Mass.):—I should like to take this opportunity to congratulate Dr. Smithwick on his excellent study. The amount of tedious, time-

consuming work involved in such a set of experiments is well known to all of us. All clinical and experimental students of the ulcer problem will be grateful for these efforts.

There are three phases of the work that I should like to discuss briefly.

Since splanchnicectomy permits the vagus nerve to act unopposed on the stomach, many observers have felt that such an operation would foster the development of peptic ulcer. There is some experimental evidence to corroborate this view, and, in fact, there is some clinical evidence which would seem to prove the same. Mason and Pollard have recently reported thirteen such cases. In practically all these cases, however, an ulcer had been present preoperatively and had merely recurred postoperatively. These postoperative ulcers, however, were more serious than the usual peptic ulcer in that two of them were fatal and the others were complicated by hemorrhage, perforation, or penetration into the pancreas.

Similar cases, wherein preoperative peptic ulcers recurred in more complicated form postsplanchnicectomy, were reported by Blegen and Kintner in the Journal of the American Medical Association in which the patient had severe hemorrhage, and by Weeks, Ryan and Van Hoy, also in the Journal of the American Medical Association, in which the patient died from a perforation.

It would appear from the studies just presented by Dr. Smithwick that vagal predominance is not the cause of such postsplanchnicectomy peptic ulcers. He showed that splanchnicectomy does not augment the hydrochloric levels except for a minor rise in total acid unit time following the insulin test. It is important to note a drop, rather than a rise, of 68 per cent in the basal total free acid, a 33 per cent drop in the broth (physiological chemical stimulus) total acid, and a 44 per cent drop in the histamine (potent chemical) response.

It thus appears probable that the severity of postsplanchnicectomy peptic ulcers is due to a disturbance in the pain pathways produced by the operation. The absence of the typical ulcer pain gives the patient little knowledge of his ulcer and hence he does not treat himself adequately.

The second point to be discussed has to do with the difficulty in correlating such experimental studies with clinical studies. For instance, the author made the statement that the response of the stomach acidity to broth (the physiological chemical stimulus) is an important criterion of ulcer protection. Their figures for gastric resection show the total acid response to broth to be reduced 96 per cent when the antrum alone was resected, and 95 per cent when the resection was three-quarters to four-fifths. This would seem to prove that both procedures would give the same ulcer protection. We know clinically and experimentally, however, that such is not the case. The stress and strain of life are obviously more potent gastric stimuli than such experimental ones.

The third and last point to be discussed has to do with the addition of vagectomy to gastrectomy. The addition of vagectomy to 50 per cent resection reduced the response to all the stimuli very markedly and vagectomy plus four-fifths

gastrectomy reduced the response to a maximum degree. Thus this work gives experimental support to the numerous clinical studies on vagectomy as a treatment for gastrojejunal ulcers.

I should like to ask Dr. Smithwick whether he would discuss briefly the mode of action of splanchnicectomy in reducing the acid response.

Discussing this paper has been a great privilege and I should like to thank the Association for that privilege.

Dr. Reginald H. Smithwick (Boston, Mass.):—I wish to thank Dr. Byrne for his discussion. I am inclined to agree with him that any untoward effect which splanchnicectomy may have on ulcer patients is not due to an increase in the hydrochloric acid production but, as he pointed out, in all probability is due to a decrease in pain, so that the patients are not aware of their ulcer and do not handle themselves accordingly.

Certainly from these data that we have, there is no reason to feel that because you cut the sympathetic division that the parasympathetic will become overactive in so far as gastric secretory mechanisms are concerned. It is true that we generally think of the two divisions of the autonomic nervous system as being opposed, and certainly so far as gastric motility is concerned, there is a very marked alteration, particularly when the vagus is sectioned, but this opposed activity of the two divisions apparently does not carry into the secretory mechanisms of the stomach.

In regard to the possible explanation for the reduction in acid following splanchnicectomy, the only suggestion I have at the present time is that we have apparently three chemical mediators of gastric secretion: acetylcholine, representing the vagus; sympathin, or some such substance, representing the sympathetic; and gastrin, a substance derived from the antrum. Figures such as I have presented tend to make you suspect that these various chemical mediators potentiate each other; that sympathin probably potentiates the action of gastrin and also of acetylcholine, and that when one of these three substances is removed, the other two are less effective in its absence than they were before.

We hope later on in these experiments to try to replace what we have removed; that is, to lower the gastric secretion by removing one or more factors, and then to replace them by giving the patient drugs which have a peripheral action and replace what we have taken away. I think if we are able to do that, we probably can explain just how these various factors act singly and in combination.

CANCER OF THE LARGE BOWEL — OPERATIVE CONSIDERATIONS*

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Cancer of the large bowel rates high as a site of malignancy. It seems to be on the increase; but it can be diagnosed early, and it can be cured by surgery. In well-screened clinics[1] over 80 per cent of the patients with this disease are found to be resectable, while 50 per cent may expect 5-year cures with over-all mortality of less than 5 per cent.

Unfortunately, in the Boston City Hospital many of our patients are still admitted with large inoperable tumors or acutely ill with intestinal obstruction. A review of their histories practically always reveals that they have had at least one of the typical symptoms of cancer of the lower bowel for over a year. Either bleeding by rectum, change in bowel habits, or abdominal pain is almost invariably present. The medical profession must also accept some of the blame for late diagnosis. Every doctor should remember that over 50 per cent of the cancers of the rectum can be felt by digital examination; 100 per cent of cancers of the rectum can be seen with the sigmoidoscope, and 90 per cent of malignant tumors of the large bowel above the vision of the sigmoidoscope can be diagnosed by proper x-ray technic.

The cure of colonic malignancy can be approached with considerable optimism as long as we remember that each case has two problems. First, can the patient stand the operation? Second, can the lesion be completely removed?

The proper preoperative and postoperative care of the patient is absolutely essential, and with this, all surgeons interested in this problem are in agreement. To Dr. Wangensteen[2] belongs the major credit for bringing to our attention the effects of obstruction, both acute and chronic, upon the vital functions of the individual. The relief of the obstruction in some manner must precede our attack upon the underlying malignancy. Hypoproteinemia, avitaminosis, anemia, and other biochemical disturbances are looked for and corrected. In 1939 Garlock and Seeley[3] reported the effect of oral sulfonamide on intestinal bacteria. There seems to be nearly universal agreement that chemotherapy and antibiotics should be used preoperatively and probably postoperatively to aid in the prevention of infection.

Good anesthesia, free use of blood, and maintenance of fluid and electrolyte balance are now known to be necessary if we expect a satisfactory postoperative course.

Assuming that the patient has been properly prepared for the operation, the complete removal of the cancer is based upon:

(1) The knowledge of the anatomy involved by the lesion.

(2) The understanding of the pathological processes.

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(3) The application of the technical procedure best suited for the individual case.

Anatomy

The colon represents about 25 per cent of the length of the whole intestinal canal, and its diameter gradually diminishes from the cecum to the sigmoid. The right and left colons differ greatly. The ascending colon and right half of the transverse colon develop from the midgut, and in a way simulate the function of the small bowel, that is of assimilation and absorption. The left half of the colon is derived from the primitive hindgut. It functions as a place for storage and expulsion.

In Singleton's[4] excellent article on "Blood Supply of the Large Bowel", he explains that the circulation to the large bowel is from three major sources.

(1) Superior mesenteric artery with its ileocolic, right colic, and mid colic branches supplying the large bowel from the cecum up to the region of the splenic flexure.

(2) Inferior mesenteric artery with the branches, left colic, sigmoidal, and superior hemorrhoidal furnishing the blood supply for the remainder of the large bowel.

(3) The rectum, however, is supplemented by branches from the internal iliac artery consisting of the middle hemorrhoidal, inferior hemorrhoidal, and the pudic branch.

Blood reaching the colon passes from the above-mentioned main arterial trunks to the marginal artery of Drummond, with its vascular loops and vasa-recti, to the blood vessels within the bowel wall.

Singleton points out that even if there are no anomalies, the blood supply of the colon is easily jeopardized if the vasarecti are injured because of lack of free collaterals. Because the blood supply of the colon is central, so to speak, it allows division of lateral peritoneal attachments without the danger of interfering with its blood supply. This is extremely important and in a way perhaps equalizes the great care that must be exercised as we approach the bowel from the mesenteric side.

In surgery of the colon we should apply this knowledge by first freeing a minimum of the mesenteric attachment just adjacent to anastomosis. Second, lateral anastomoses should be done on the antimesenteric border. Third, clamps should be applied at a slight angle so that optimum circulation can be maintained. Fourth, appendix epiploica should be preserved if possible.

The venous return follows the arterial supply through the portal system to the liver.

Lymphatic vessels ordinarily follow the arterial supply. In 1909 Jamieson and Dobson[5] described the paracolic lymph nodes located along the arcades on either side of the tumor. The usual drainage is from these glands to the intermediate glands about halfway between the arcades and the main glands, which are practically always found at the origin of the main arterial trunk.

It is, therefore, obvious that an adequate operation for cancer requires removal and ligation of the arteries as near as possible to the main arterial trunk if we expect to remove all the lymph nodes.

In the lower rectum the lymph drainage is not only upward along the course of the superior hemorrhoidal artery but also laterally along the course of the middle and inferior hemorrhoidal arteries to the hypogastric nodes and at a lower level near the skin follows the superficial lymphatics to the inguinal nodes.

Pathology

Cancer of the large bowel spreads in the three typical and well-recognized manners either by local invasion, through the lymphatics or blood supply.

The operating surgeon can usually diagnose by palpating cancer of the large bowel. However, gross pathology may be extremely difficult to interpret, even for a well-trained pathologist, as to whether the lesion is cancer, and if it is, how much of the tumor is inflammatory reaction. The presence of adjacent lymph nodes does not necessarily mean that they contain cancer. A nodule in the liver, which may well be a visceral metastasis, does not preclude a radical attack upon the local lesion.

What has the pathologist taught the surgeon? First, the types of carcinoma. The most common type of carcinoma is the adenocarcinoma. On the left side of the bowel it may well contain those elements identifying it as a scirrhous type. This characteristic encircling of the bowel takes approximately twelve months. The colloid type of carcinoma is not as common but much more malignant, and when the so-called signet cells containing mucin are found, the ultimate prognosis is very grave. Broder's classification of cancer as to grade of malignancy is not very helpful in determining the ultimate prognosis of tumors in the large bowel. The size of the tumor has no relationship to its malignancy or whether or not it has metastasized. In a general way the larger tumor indicates a process, which has been developing for a long time, but strangely many of the very large tumors, which at first hand appear to be inoperable, have later been found to be very slow growing without any gland or vascular involvement.

The local spread of the cancer in the bowel itself is extremely important in determining the extent of the resection. Although Black and Waugh[6] concluded that the greatest longitudinal spread was in the submucosa and in none of their cases extended more than 2 centimeters into the normal bowel from the obviously macroscopically involved bowel, from a practical viewpoint it is felt that at least 4 centimeters of normal bowel should be removed above and below the lesion.

Nickell and Dockerty[7] in a study of 5-year survival rate on individuals, who had had a resection of a tumor following a complete obstruction, found that the prognosis for a 5-year cure was 26 per cent instead of the expected 50 per cent due probably to damage of the intestinal wall and subsequent breaking down of the host protective mechanism, which attempts to locally contain the malignant process.

Although it has been recognized for many years that cancer spreads through the lymphatics, the exact nature of this is still not clear. Gilchrist and David[8] have studied this problem perhaps more completely than anyone else. They seem to feel that the lymphatic spread seems to follow a typical pattern and is primarily embolic. The spread is almost invariably upward, but not always, and when the lymph node is completely overwhelmed, the spread then may be through collaterals and even retrograde if there is a marked obstruction to the lymph flow. Lymph nodes are often involved before the carcinoma cells have penetrated from the mucosa to the serosal layer of the bowel. In a general way it may be stated that when lymph nodes are involved with tumor, the prognosis is 50 per cent as favorable as when the lymph nodes are not involved. Gilchrist and David's study of 10,000 lymph nodes in 200 specimens of patients, who lived over 5 years, found that the survival rate seemed to be higher with lesions on the right side of the colon as compared to the left probably because of a wider resection of node-bearing mesentery. When the cancer developed below the peritoneal reflection as in the rectal area and there were gland metastases, the prognosis was 25 per cent or much lower than when the glands occurred from a lesion above the peritoneal reflection.

Venous spread may occur in any stage of the disease. It may occur extremely early before the patient has any local evidence of his disease. It is generally found in about 15 per cent of lesions of the large bowel. When involvement of the veins can be found by microscopical study, the 5-year survival rate drops from the expected 50 per cent to 15 per cent. Tumor cells invading the veins spread through the portal system to the liver, and the work of Batson explains the occasional occurrence of bone metastases and metastases in other organs.

From the standpoint of pathology undoubtedly the most important contribution to the management of cancer of the large bowel is the definite proof that cancer rises very commonly from adenomatous polyps. In a general way it might be stated that all polyps in the lower intestinal canal are premalignant. Early identification and removal of these tumors in this premalignant stage cannot be too strongly stressed.

Surgical Technic

Although M. Reybard, a French surgeon of Lyons, France, resected a malignant tumor of the sigmoid and performed a successful end-to-end anastomosis in 1833, it was not until nearly 100 years later that this operation became a common procedure. M. Reybard was unaware of Lembert's method of suturing bowel, and I believe that his suture should really be considered the beginning of intestinal surgery. Today there are over 250 methods of intestinal anastomosis, of which 45 are described as being of the aseptic type. Although palliative colostomies were occasionally performed in the nineteenth century, there was little enthusiasm to attempt removal of a malignant tumor because of the high instance of peritonitis. This complication was partially controlled by various exteriorization operations first described by Bryant and later by Block and Paul, but really popularized in

1898 by Mikulicz.[1] With this operation the mortality dropped from 50 to 15 per cent, but there was a high incidence of local recurrence of the tumor at the site of operation. In 1930 Dr. Rankin[9] described an obstructive type of operation carrying with it certain features to diminish the danger of local recurrence and still be considered a "safe" operation. During the past ten years, however, most surgeons have preferred a primary resection with either an open or closed anastomosis in uncomplicated tumors extending from the cecum to the rectosigmoid. Unfortunately, in the Boston City Hospital many malignant tumors appear in an obstructed condition, and in such an instance this obstruction must first be relieved before an attack can be made upon the local lesion. The intestinal tube will be of no value in the individual with a competent ileocecal valve and a vent proximal to the obstruction must be performed as early as possible. An ileocolostomy, cecostomy, or transverse colostomy is performed depending upon the site of the lesion. Then at a later date a resection and primary anastomosis may be attempted. If the local tumor is considered inoperable because of its infiltration into contiguous organs, a side-tracking operation, in preference to an abdominal colostomy, is attempted assuming that there is bowel distal to the tumor that can be utilized for an anastomosis. If the tumor is locally resectable, and exploration shows the presence of liver metastasis, an attempt should be made to remove the tumor and perform an anastomosis.

In 1908 Miles described an abdominal perineal resection of tumors of the rectum and rectosigmoid regions, and this operation is still in widespread use. In the past few years much has been written about establishment of bowel continuity following removal of malignant tumors in the rectum. In this hospital we feel that anterior resection and anastomosis for tumors in the rectum should not be performed unless the lesion is freely movable, of low malignancy, apparently early, and located at least 14 centimeters above the anus. However, if metastatic liver disease is found, and the tumor seems to be locally resectable, an attempt will be made to remove the tumor and perform an anterior anastomosis even though it is situated at a much lower level.

The basic principles regardless of the type of operation are the same if a curative cancer operation is to be performed.

(1) The optimum exposure of the pathology and involved bowel through
   (a) Good anesthesia.
   (b) Adequate incision.
   (c) Mobilization of the bowel.
(2) Adequate removal of the tumor with the lymph bearing area.
(3) Proper anastomosis of the bowel.
   (a) Free blood supply to both segments and especially at the line of suture. Free bleeding should be demonstrated at the line of suture.
   (b) Careful approximation of the segments in two layers, an inner layer interrupted using fine catgut on an atraumatic needle turning the mucosa in without the formation of a diaphragm, an outer serosal

layer using interrupted fine silk or cotton on an atraumatic needle likewise taking care not to turn in a diaphragm, not to penetrate the mucosa, and not to tie the knot too tightly. This is the important layer and the serosal layers must be in absolute contact throughout the entire circumference of the anastomosis.

(c) Avoidance of tension on the suture line.

(4) Proximal decompression if there is any question of

(a) Increase in the intraluminal pressure from unrelieved obstruction.

(b) Poor blood supply at the site of anastomosis.

(c) Possible tension at the suture line.

At the present time in this hospital there seems to be a swing toward the open type of anastomosis as we feel that we can be a little more sure about the blood supply and a well approximated suture line. We believe that peritonitis and other serious complications, which may locally occur, are due not to contamination from open suture, but are due to failure of the suture line to hold.

In conclusion it is obvious that I have stressed the relationship of only two of the basic sciences, anatomy and pathology, to our present-day approach to cancer of the large bowel. All the other sciences are just as important.

Surgical removal is the only method of cure of cancer of the large bowel, and the surgeon, who performs the operation, has only one opportunity to cure his patient. The responsibility of the surgeon is great for he must not only safeguard the patient's life, but he must completely remove every cancer cell when he performs his operation.

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ULCERATIVE COLITIS*

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There are many serious problems that challenge the judgment of both the internist and the surgeon in the management of ulcerative colitis. These are massive hemorrhage, perforation with resulting peritonitis or abscess formation, severe toxemia with or without the toxic manifestations of pyoderma, joint involvement or iritis, the development of fistulas, the presence of varying degrees of intestinal obstruction, superimposed malignancy in a bowel already devastated by advanced inflammatory changes, and the determination of the optimum time for performing ileostomy. In the brief time at my disposal, I shall not attempt to discuss the various phases of this dread affliction. Instead, I should like to consider two specific instances of ulcerative colitis designed to demonstrate the type of management not commonly advocated in the surgical treatment of this disease in the hope that the benefits of surgery might be further expanded, if the procedures suggested are judiciously applied to other carefully prepared and properly selected patients.

Case 1:—F.S. A 38 year old white housewife who was first admitted to the hospital in February of 1939 with a 2½ year history of periodic attacks of diarrhea consisting of ten to twelve daily stools containing blood, mucus and pus and associated with abdominal cramps and tenesmus. She suffered recurrence of symptoms approximately every six months, lasting from two to four weeks. Barium enema at that time showed slight changes in the descending colon consistent with early ulcerative colitis and sigmoidoscopy revealed mild changes of ulcerative colitis in the rectum with evidence of blood and mucus coming down from above, suggesting upward migration of the active process in the rectum to the descending colon. During a period of 27 days of hospitalization in February and March of 1939 two transfusions of blood were administered to correct a moderate anemia. She ran a persistent slight elevation in temperature and her pulse varied between 110 and 120. She improved slowly and at the time of her discharge she was having one to two semi-formed stools without blood, mucus or pus. She was afebrile and felt quite well. During the subsequent seven years she averaged two to three flare-ups of her colitis yearly which confined her to bed from two to six weeks with each attack. In the intervals between the attacks she enjoyed reasonably good health.

Early in August of 1946 she suffered a relapse of greater severity. Abdominal cramps and tenesmus were frequent and severe, and she averaged fifteen to twenty movements daily mixed with blood, mucus and pus. She was hospitalized in August of 1946. At the outset of this attack her temperature and pulse reacted only slightly, but beginning with the eleventh hospital day her temperature rose to

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between 101 and 103°; the white count was 22,000 and her pulse rose from 90 to a level ranging between 120 and 130. Her red count, which was 4,800,000 on admission, gradually fell to 3,500,000 and a hemoglobin of 90 dropped to 70 despite several transfusions of blood. Rectal bleeding began to assume massive proportions. Diffuse abdominal pain with marked tenderness developed in the mid- and left upper quadrants of the abdomen and it was feared that she had a slow perforation of the descending colon. Despite huge doses of penicillin and streptomycin her condition became critical with a temperature of 104° and a pulse rate of 140. Accordingly, one month after her admission to the hospital a double-barreled ileostomy was performed. During the first 48 hours her improvement was encouraging. Her temperature fell from 104 to 99° and her pulse from 140 to 110. However, rectal bleeding soon recurred with increasing severity and her pulse and temperature both became elevated again. Twelve days following her ileostomy she developed signs of bilateral deep thrombophlebitis of the legs with clinical and x-ray evidence of pulmonary infarction, for which both femoral veins were ligated. The signs in the chest gradually resolved but her rectal bleeding persisted and became alarming. Her pulse fluctuated between 130 and 150 and her temperature was 103°. Her blood pressure, which at one time fell to 90/70, was restored to an average level of 120/80 by multiple transfusions of blood and plasma. She received a total of 41 transfusions of blood during this acute period of her illness. It was felt that her only chance for survival was colectomy. The grave risk of surgery in a patient so critically ill was fully appreciated. Three weeks after her ileostomy, subtotal colectomy as far down as the lower sigmoid was performed. Since it was demonstrated by sigmoidoscopy that the source of bleeding was above the rectosigmoid, there was no valid reason for further adding to the risk of surgery by also removing the rectum in a patient in extremis. The resected colon showed extensive involvement with the mucosa ulcerated beyond recognition. She responded very well to surgery with her temperature returning to normal in ten days and remaining so. She was discharged on the 29th postoperative day with a good functioning ileostomy. At the end of eight months she had gained forty pounds in weight which she has maintained up to the present time and her general condition has been excellent. Her adjustment to the ileostomy with the aid of a Koenig-Rutzen Bag has been most gratifying. On rare occasion the rectum has shown a minimal degree of activity and the appearance of the mucosa on sigmoidoscopy, while much improved, does not justify an attempt to re-establish intestinal continuity."

Comment:—It is well recognized that many patients with ulcerative colitis are subject to recurrent bleeding. The purpose of presenting this case report is to emphasize the less common, but grave and dangerous, complication of unremitting massive hemorrhage. Without radical surgery a fatality would have been inevitable in this patient. Ileostomy alone was unavailing. It seldom can be relied upon to control the complication of recurrent episodes of bleeding in ulcerative colitis. There is certainly no reason to expect that ileostomy should prove beneficial in

arresting massive bleeding from a badly diseased colon. A tendency to recurrent bleeding, resulting in moderate anemia and requiring periodic transfusions to maintain a satisfactory blood level in a patient with x-ray evidence of advanced structural changes in the colon, is a justifiable indication for elective radical surgical intervention. This patient particularly demonstrates the need for a bold and aggressive attitude when confronted with uncontrollable massive hemorrhage. Although an extremely hazardous undertaking, subtotal colectomy may prove life-saving. In such a patient one is compelled to carry out subtotal colectomy combined with ileostomy as the initial procedure, because of the futility of ileostomy alone. It is probable that this patient would have been a less hazardous risk for combined subtotal colectomy and ileostomy at the time of her preliminary ileostomy three weeks previously.

Case 2:—M.P. This is a 17 year old girl who was first hospitalized in 1941, at the age of eight, for a period of five weeks because of abdominal cramps, frequent watery bowel movements and a mild febrile reaction. She was subsequently readmitted to the hospital on five different occasions for periods varying from three weeks to two months with increasing symptoms and signs of colitis. Sigmoidoscopic and barium enema studies were at first negative but on later hospital admissions disclosed findings consistent with advanced ulcerative colitis and polypoid changes most marked in the left colon. Her current hospital admission began in July of 1949 when she entered with a history of severe generalized abdominal cramps associated with nausea and vomiting and a marked febrile reaction. Her pulse rate fluctuated between 110 and 130. She had six to ten loose movements daily with mucus, pus and blood. She also complained of a good deal of pain in the region of the right hip and perineum which was relieved following the evacuation of a large abscess of the right labia. On sigmoidoscopy the rectum appeared edematous and hyperemic. Her barium enema showed a rigid colon with evidence of scattered superficial mucosal ulcerations and polyposis most marked in the left colon. After two weeks of parenteral alimentation with proteins, vitamins and blood, together with the administration of antibiotics, she failed to gain in weight, strength or appetite. Purulent drainage from a persistent perineal fistula was still in evidence. Because of cumulative x-ray evidence of increasing and irreversible structural changes in the colon and the development of a persistent perineal fistula in a patient who exhibited clinical evidence of an unyielding nutritional deficit, radical surgery was deemed advisable. Since she was not in an acute fulminating phase of the disease it was felt that she could tolerate a one stage subtotal colectomy in combination with ileostomy. In August of 1949 an ileostomy combined with subtotal colectomy was performed in one stage. She tolerated surgery remarkably well and her postoperative course was likewise very favorable except for the need of revising her ileostomy five weeks later because of intermittent obstructive manifestations.

Comment:—In discussing this case report I should like to concern myself chiefly with the question of the safety and feasibility of ileostomy combined with

subtotal colectomy as a one stage procedure in carefully selected patients. The satisfactory response to this type of operation performed in this patient suggests that it might well be applied in other instances of properly selected and carefully prepared cases of ulcerative colitis, as opposed to the more commonly advocated multistage procedures on the remaining diseased colon following preliminary ileostomy. This type of surgical approach is not recommended for all patients who have become intractable to medical treatment. No single operative procedure can be exclusively employed in the surgical management of a disease so unpredictable in its course and with so many variable clinical patterns. There are those patients in whom the clinical picture is that of essentially severe and prolonged toxemia manifested by persistent fever, an elevated pulse rate, unremitting diarrhea and abdominal tenderness with varying degrees of distention in whom sepsis and nutrition cannot be satisfactorily improved preoperatively. If surgery is contemplated in such an instance, it is unwise to risk more than a preliminary ileostomy. On the other hand, there are a significant number of patients who have been seriously ravaged by repeated exacerbations of the disease in whom the colon has undergone advanced and irreversible structural changes. They are often further invalided by such complications as anemia through slow but continuous blood loss, nutritional changes of the skin, polyarthritis and the development of perianal fistulas, as was the case in this patient. They become seriously and chronically debilitated invalids. It is this type of patient who may be better prepared to tolerate a major surgical ordeal and also be fortified against such serious postoperative complications as peritonitis and surgical shock by supplying and maintaining adequate preoperative nutritional requirements through the proper utilization of blood, plasma, proteins, vitamins, and electrolytes, as well as the newer antibiotic and chemotherapeutic agents. These newer advances have been of epochal importance in reducing operative morbidity and mortality. Granting that neither streptomycin, penicillin nor aureomycin can be expected to exert any consistent action on chronic ulcerative colitis, these pharmacologic agents, however, may prove to be of inestimable value in controlling or arresting the advance of a local or spreading peritonitis from a perforation of the bowel. Ileostomy in the presence of such a fulminating complication carries a prohibitive mortality rate and should be avoided. Ileostomy during a rapidly progressive toxic exacerbation of the disease probably accomplishes nothing which cannot be achieved with an equal chance of success by the proper use of the available antibiotic and chemotherapeutic agents, coupled with adequate parenteral alimentation. One of the important factors for the sharp reduction in the overall mortality figures in the surgical therapy of ulcerative colitis has undoubtedly been the avoidance of ileostomy during the critical acute phase of the disease.

It is suggested that subtotal colectomy combined with ileostomy as a one stage procedure may be suitably adapted for other patients whose clinical course is comparable to the one just presented. Dr. G. Gavin Miller and associates[1] recently reported on six patients in whom ileostomy together with right hemi-

colectomy was performed with uniformly good results. They expressed the opinion that with proper preoperative preparation ileostomy with right hemicolectomy can be done with a lower mortality than a simple ileostomy. They believe that in addition to the benefits derived from the removal of the right colon which may be regarded as a focus of toxic absorption, this type of operative procedure eliminates one stage in the process of total colectomy. Our recent encouraging experience with this type of surgical approach suggests the feasibility of its application to other comparable carefully selected patients.

Conclusions

1. Massive hemorrhage threatening life and not responding to heroic attempts at blood replacement calls for an aggressive surgical attitude. Subtotal colectomy becomes imperative even at the serious risk of a mortality. Whenever possible colectomy should be resorted to before bleeding becomes alarming.

2. It is suggested that subtotal colectomy in conjunction with ileostomy as a one stage procedure may prove to be of value in the surgical treatment of properly selected and carefully prepared patients with chronic ulcerative colitis.

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FACTS AND PROBLEMS OF HEPATITIS
(PART I)

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The conception of hepatitis has changed greatly in the last decade. According to the orthodox definition, any inflammatory process is confined exclusively to the connective tissue, while the parenchyma has no direct share in the inflammatory reaction and in the biological defense. It has, however, been proven beyond doubt that in the liver, not only the reticuloendothelial cells (Kupfer cells), but also the very liver cells take part in the defense reaction when an infectious or toxic injury invades the organ. Cooperation between the Kupfer cells and the liver cells exists, not only in the daily work of biochemical functions, as, for example, in hemoglobin bilirubin metabolism, but also in times of danger during an attack by toxins or bacteria. The defense work done by the epithelial cells consists in phagocytosis of bacteria and antitoxic defense measures. When bacteria are injected intravenously, the germs disappear quickly from the bloodstream, but they may be cultivated for a long time from excised specimens of all parts of the liver where they have been arrested and rendered innocuous, though still viable. In a series of 245 cases (Gundermann[1]) of gallbladder disease staphylococci were cultivated from the liver in 108. Considering the frequent presence of germs in the liver, the formation of abscesses and the anatomical changes regarded as characteristic of fully developed inflammation, are rare. This, according to Roessle[2], is due, not only to the high efficiency of the reticuloendothelial cells, but also to the epithelial defense apparatus. In inflammation of all parenchymatous organs two processes can be distinguished: the actual inflammatory reaction and the degenerative changes in the epithelial cells. These processes may or may not parallel one another.

It is acknowledged that the normal liver cell has certain protective powers against invasion by disease processes. Before the pathological process can be established by virus or bacterial infection, it is necessary to break down the resistance of the liver through antecedent damage which is brought about by various substances or processes. These may be enumerated as alcohol excess, protein deficiencies, precedent toxic damage through the use of arsenicals, malaria, pregnancy, nutritional intoxication, and may be regarded as the leading conditions which give rise to diminished resistance on the part of the liver cell, rendering the soil fertile for the seed of bacterial infection to become active. The seed may be an infection, but in order for it to grow, the soil must be prepared by the fertilizer in the nature of agents producing precedent liver damage (Hampson[3]). Fiessinger[4] formulated these observations as follows: "It is the first damage which suppresses

Ed. Note:—This is the first of a series of four papers on Hepatitis which will be published in THE REVIEW OF GASTROENTEROLOGY during the year.

the defense against the second attack." For years it was our aim to study and analyze these sensitizing or fertilizing factors in all cases of hepatitis (Pribram[5]). In the various forms of epidemic hepatitis, serum hepatitis, acute atrophy of the liver, and cirrhosis we found good reason to believe that the first sign of liver damage often has a marked allergic character, and in certain groups of hepatitis this allergic element could be traced and established. These observations find their expression in the classification we are trying to present.

CLASSIFICATION OF HEPATITIS

I. *Allergic Forms:*
   1. Allergic edema
   2. Serous hepatitis
   3. Lymphangitis hepatica

II. *Destructive Forms:*
Acute infective hepatitis: acute yellow atrophy, nodular cirrhosis.

A. *Viral Infections:*
   (1) *Epidemic Hepatitis* (high infective virulence):
      (a) Respiratory tract entrance (contact infection)
      (b) Alimentary tract entrance
      (c) Parenteral infection
         Type: Yellow fever (by insects as hosts)
   (2) *Sporadic Form:* (low infective virulence—No contact infection):
      (a) True catarrhal jaundice: Sensitizer important (food poisoning)
      (b) Serum hepatitis (parenteral infection only)

B. *Leptospiral Infection:*
Type: Hepatonephritis
(Weil's disease)

C. *Cholangitis Type:* (Nonspecific)
   (1) *Primary Hematogenous Infections:*
      (a) Type: Typhoid, paratyphoid, Coli group
      (b) Pneumococci, streptococci, etc.
      Recurrent fever, etc.
   (2) *Secondary:*
      (a) Common complicating hepatitis in gallstone disease
      (b) Ascendant infection following duodenitis

D. *Toxic Hepatitis:*
Anorganic and organic poisons

Allergic Edema:—This condition is best understood if it is borne in mind that allergic manifestations in general consist in the development of a local edema, sometimes of explosive character, the result of toxic damage of the capillary walls, which leads to an increased permeability. While this variety of edema appears suddenly, it may subside as quickly as it appeared thus showing the significance of these conditions; that is, their fleeting character.

During digestion, a certain enlargement of the liver is physiologic. It appears that the liver possesses the ability and physiologic function to store fluids which are absorbed from the intestines and to gradually release them into the general circulation in amounts approximately equal to the urinary output. This storage of water in the liver prevents a digestive flooding and dilution of the blood and aids in maintaining normal blood volume. The mechanism of this "physiologic edema" is not definitely established. The retaining water probably is partly interstitial in the perivascular spaces and partly intracellular where intermediary products of

metabolism, such as lactic acid and others, displace the cellular pH to the acid side and increase the water affinity of intracellular colloids (Fig. 1).

Pathologic edema of the liver is observed, not only as collateral edema in practically all acute gallbladder conditions, but also in various unrelated diseases where it has been found to occur in 15 per cent of cases, whereas in control series of normal persons killed by violence, no instance of hepatic edema was present (Keschner and Klemperer[6]). It is important that these pathologic conditions be clearly differentiated from diffuse acute allergic edema, which is intimately related to the absorption of certain foodstuffs which reach the liver by way of the portal vein and perhaps the lymphatics also. A person takes certain foods or drugs

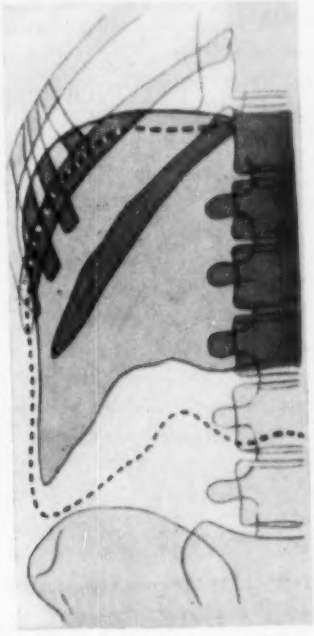

Fig. 1—Physiologic liver edema during digestion. The liver cells contain large fat droplets, vacuolized by water which apparently has diffused from the intercellular spaces through the cell membranes. This intracellular edema seems to be of very recent origin, while the fatty degeneration certainly is older. The Disse spaces are not enlarged, as is the case in serous hepatitis, but, on the contrary, they are narrow and apparently compressed as a result of edematous enlargement of the cells. This edema should, therefore, not be confused with the albuminous effusion into the Disse spaces in so-called serous inflammation.

that do not agree with him, or, to put it another way, to which he is allergic. Clinical syndromes of acute indigestion, such as nausea and anorexia, develop, and the patient complains of some tenderness and pressure in the right upper quadrant of the abdomen. The liver is found to be enlarged, often extending four finger breadths below the costal margin, it is soft in consistency and only slightly tender, in contradistinction to the painful congestion of the organ due to acute cardiac

failure. The development of the edematous liver frequently occurs abruptly, in an explosive way analogous to the liver phenomenon in anaphylactic shock. The liquid is watery and in contradistinction to the effusion in serous inflammation, discussed below, does not contain any albumin. The albumin-globulin ratio in the serum is not disturbed, the number of red blood cells is relatively increased through hemoconcentration, eosinophilia is significantly high, up to 6 to 10 per cent. The edema may disappear as quickly as it came, due to the fact that it is readily reabsorbed in the blood stream. The disappearance of this edema can be greatly accelerated by the injection of a 50 per cent hypertonic dextrose solution. In most cases the edema is interstitial, but in a few instances a real *intracellular edema* may be found, a most interesting feature, to which insufficient attention has been paid. The microscopic picture of such an intracellular edema is illustrated in Figure 2. Such an intracellular edema has been found also in the cells of the pancreas, showing transparency of the cells of the islands of Langerhans, caused by distention with watery fluid (Weichselbaum[7]).

When the liver is regularly examined in all instances of food allergy with distinct intestinal syndromes, edematous enlargement of the organ can be observed in many cases. This phenomenon of allergic liver edema, with its further clinical syndromes of leucopenia and eosinophilia, has been called "urticaria of the liver" (Pribram[8]), a term which has been adopted by numerous other authors. Clinically, the patients show all signs of indigestion, anorexia and nausea, a feeling of pressure in the epigastrium, flatulence, etc. The liver tests are all negative with one rather significant exception, namely, the Widal test. This test, which was originally conceived as a test of hepatic insufficiency, has to be regarded as a test for liver allergy. The so-called hemoclastic crisis with an acute drop in the number of leucocytes, together with an eosinophilia, has, in our observations, proved to be an allergic phenomenon. It has been our aim to study this test in relation to foods, other than milk in particular, to those substances to which a patient has been found to be allergic. The results obtained should stimulate further study to develop this method to a general test for food allergy similar to allergy tests on the skin.

The following case report is an interesting illustraton of acute allergic liver edema following the ingestion of freshly-baked bread, the patient having had similar episodes on several previous occasions. The allergy test used in this particular case was the original Widal test with milk.

Case Report:—Mrs. A. S., age 60 years, complained of a sense of discomfort in the epigastric area and a feeling of distention, starting two days prior, following an "indifferent" meal. She recalled, however, that some time previously she had had exactly similar symptoms following the ingestion of freshly-baked, warm bread. On the present occasion the patient had partaken of the bread two days previously. Ten days preceding the present illness she had an attack of influenza and as a result was quite run down in health.

Upon examination the liver was found to be greatly enlarged, the right lobe extending more than a hand's breadth below the costal margin. It was soft in

consistency. The urobilinogen test in the urine was strongly positive; the bilirubin reaction showed traces. The Widal test, done with 200 cc. of milk, disclosed a reduction of the white blood cells from 7,700 to 6,100, with a rise in the eosinophiles from 5 to 9.6 per cent.

Treatment consisted of the intravenous injection of 10 cc. of a 50 per cent glucose solution and 10 cc. of a 10 per cent saline solution. Within twenty-four hours the liver had decreased considerably in size. After forty-eight hours all clinical signs had disappeared and no enlargement of the liver could be noted. At this time the patient expressed herself as hungry and felt perfectly well. The urobilinogen in the urine was scarcely increased and the eosinophiles had dropped from 9 per cent to 5 per cent.

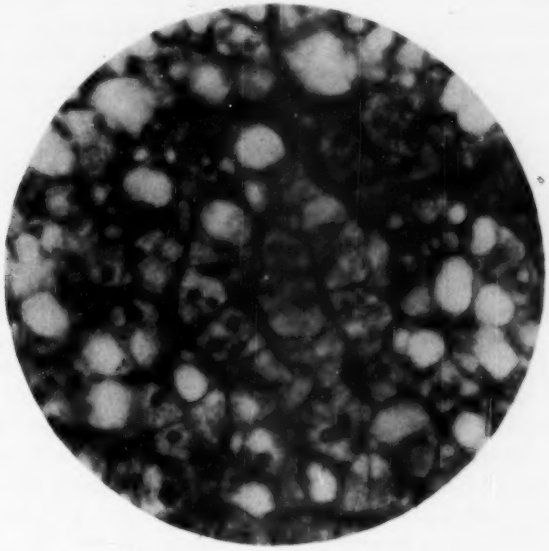

Fig. 2—Intracellular hepatic edema.

Liver conditions related to food allergy can successfully be treated by "desensitization". This was described by Pribram[9] in 1922. This form of treatment consists of intravenous injections of nonspecific proteins, which cause some fever reaction.

We are of the opinion that allergic hepatitis is a disease of much more frequent occurrence than is recognized by the profession at large, and that it might be a predisposing factor in the development of more destructive forms of hepatitis.

Serous Inflammation:—In the conditions just described, damage to the walls of the capillaries, is of moderate degree only. Nothing but water containing a few electrolytes penetrates the pericapillary spaces and the membranes of the liver cells, giving rise, in some instances, to an acute intracellular edema in addition to

the interstitial edema. In the event that this damage to the walls and membranes through the action of more toxic agents, becomes more pronounced, not only water and electrolytes, but colloids of all varieties penetrate the pericapillary spaces. It has been demonstrated by Krogh[10] that the permeability of the capillaries in a state of toxic paralysis is distinctly increased and, reaching a certain degree, become permeable, not only for substances in solution, but also for substances as large as starch particles. Serum albumin is the most noteworthy substance to penetrate the pericapillar (Disse) spaces, thus giving rise to an albuminous effusion of distinct inflammatory character, a feature which has been termed serous inflammation (Roessle[11]), (Eppinger[12]). This effusion between the liver cells and capillary walls, stainable with eosin, acts as a separating and isolating layer and may interfere seriously with the metabolic exchange of gas and the nutritional supply of the cells. This effusion, even in clinically very mild cases of acute hepatitis, may account for cell degeneration and necrosis at an early stage of the disease.

Effusion from the blood capillaries is followed by pronounced, though, at times, rapidly-disappearing changes in the blood, i.e.:

(a) Reduction in blood volume.

(b) Relative increase in the number of red blood cells (hemoconcentration).

(c) Change in the albumin-globulin ratio.

Effusion in serous inflammation of the liver never reaches the degree that it does in fleeting edema. In the latter condition the liver is sometimes only slightly enlarged; the diagnosis of serous inflammation is actually microscopic rather than clinical.

An important fact is that, in contrast to fleeting edema, this albuminous *effusion is not reabsorbed into the blood capillaries, but is slowly drained away with the lymphatics*. This fact forms the fundamental distinction between simple fleeting *allergic edema* and this form of *inflammatory effusion*. It alters the entire aspect of possible further development of pathologic changes in the liver. While in the case of fleeting edema, *restitutio ad integrum* without any trace is observed, within a very short time, a matter of only a few hours, the slow absorption may result in an affection of the lymphatic system of the liver and, finally, under certain circumstances, may develop into the well-defined pathological entity which we have designated *lymphangitis hepatica*.

Lymphangitis Hepatica (Pribram[5]):—Highly toxic products that drain away with the lymph stream may cause a pronounced inflammatory reaction in the entire lymphatic system of the liver, including the lymphatic glands around the extrahepatic ducts. When operating on such a case it can be observed that the liver is moderately enlarged and the surface is turbid due to the presence of a whitish subcapsular effusion. In some areas it is covered by a yellowish-white gelatinous effusion and soft fibrin. Friable, soft, edematous, gelatinous bands of fibrin run from the capsule of the liver to the peritoneal wall. In processes of long duration the subcapsular, formerly gelatinous effusions are transformed into white patches and the perihepatic adhesions are of firmer consistency.

The serosa covering the gallbladder is hyperemic. In fresh cases a gelatinous effusion is found around the neck of the gallbladder and the common duct. Freshly-formed friable, gelatino-fibrous adhesions can be seen between the gallbladder and duodenum.

Around the neck of the gallbladder and in the subserous layers one or two enlarged hyperemic lymphatic glands may be observed. These are extremely fragile and tear and bleed easily when touched with a forceps. Glands of the same character, varying in size and number, are also found around the common duct down to the duodenum. The head of the pancreas may also be enlarged at times, the result of edema and hyperplastic lymphatic tissue.

On opening the gallbladder the findings sometimes are in striking contrast to

Fig. 3—Lymphangitis hepatica

the signs of fresh inflammation in the *external* subserous layers. In some instances the finding of stones in the gallbladder seems to be quite independent of the process that takes place in the subserous spaces of the organ. The mucous membrane may show no actual signs of inflammation, but is, at times, hypertrophic, and in some cases cholesterosis may be present. Even when the wall is more or less edematous, the mucous membrane, obviously, plays only a minor role in the pathological process, or none at all. No doubt is left in one's mind that the inflammatory process did not originate in the interior of the gallbladder. Only the subserous layers are affected, the lymph spaces and lymphatic glands being the main seat of the pathological changes. The condition is one of acute hepatitis, perihepatitis and pericholecystitis, obviously originating in the liver and spreading into the subcapsular spaces. It involves the lymphatic glands around the gall-

bladder, and in many cases extends to the lymphatic tissue of the pancreas, around which greatly enlarged lymphatic glands can sometimes be seen.

To understand the nature of this disease of the lymphatics, it is well to consider it in relation to similar infections of the intraabdominal lymphatic system which has been described by one of the authors (Pribram[13,14]) as lymphangitis mesenteralis and abdominalis, including the so-called lymphangitic form of appendicitis. Since the publication of the first paper on this subject in 1925, our knowledge of this interesting disease has increased considerably through the observations of many authors in this field, as well as through further clinical and experimental work carried out by one of the authors[15].

Lymphangitis hepatica must be regarded as a localized form of the general pathological features of lymphangitis peritonealis and mesenteralis. It is necessary to recall only a few important points. These hold true for general lymphangitis peritonealis, as well as for lymphangitis hepatica in particular:

1. The lymphatics are more developed and more liable to react to toxic or infective agents in young individuals up to the age of 25 years. The lymphatic disease of the abdominal organs, therefore, prevails in younger persons.

2. A constitutional factor is frequently observed; the disease may occur in several members of the same family.

3. In all cases of abdominal lymphangitis—to use a more general term—recurrent attacks, wherever they may be localized, tend to recur.

4. There frequently is a definite relationship between these diseases and focal infection, especially in the tonsils.

5. Allergic conditions are frequently observed and have their particular clinical significance.

The following lymphangitic diseases in the abdominal cavity may be distinguished. Each has typical clinical and pathological significance:

(a) Lymphangitis mesenteralis (lymphangitic form of appendicitis).

(b) Lymphangitis hepatica.

(c) Lymphangitis pancreatica.

We have recorded 25 cases of lymphangitis hepatica altogether where the clinical symptoms and biopsy findings were characteristic, as described. Fifteen were in males and only 10 in females, a fact which seems worthy of mention because it is well known that cholecystic disease is otherwise much more common in women. Most of the patients were under 40 years of age, and a history of previous attacks was obtained, a fact which was verified by biopsy findings at operation. The youngest patient in this series was a boy of 18. The constitutional touch of lymphangitis hepatica can be illustrated by the observation that we had under our care three members of the same family, a sister and two brothers, all of them of a marked lymphangitic diathesis, with exactly the same clinical picture of hepatitis related to focal infection in the tonsils. Convincing support for the thesis of this variety of hepatitis as lymphangitis hepatica and its relation to focal

infection in the tonsils was exemplified by the sometimes dramatic results of tonsillectomy in such cases. The following is a characteristic case report:

The patient, a physician, 52 years of age, gave a history of liver trouble for years. Some enlargement of the liver was noted by all who saw him, with definite tenderness, especially during acute and subacute attacks. There were no real acute colicky pains, but there were rather slight periodic exacerbations after relatively quiet intervals, during which the patient was free of symptoms. There was loss of appetite, the bowels were constipated, and there was an increased intolerance for many kinds of food, notably fats. Repeated cholecystography revealed a fairly good gallbladder shadow with sharp contours and good emptying ability. There was no evidence of calculi. At times the gallbladder shadow was a little faint, while at others it was quite normal. Definite jaundice was never noticed, but the urobilinogen in the urine always showed an increase. The patient customarily went twice a year to Carlsbad or Vichy to undergo a strict cure, but this was followed by only slight temporary improvement.

When the patient came under observation of one of the authors he was slightly jaundiced. There were traces of bilirubin in the urine, but urobilinogen was greatly increased. The liver was enlarged and extended about three inches below the costal arch, during inspiration. Its consistency was harder than normal. There was slight tenderness all over the epigastrium, as well as in the gallbladder area, and over the right lobe of the liver. The gallbladder area showed no more tenderness than was found in the entire liver area. Pain was more pronounced on taking a deep breath, and when pressure was exerted on the liver, pain was complained of, radiating to the back. The bilirubin in the serum was slightly increased. The blood picture revealed nothing abnormal. The tonsils showed evidence of previous repeated attacks of inflammation and were slightly enlarged. A few drops of pus could be expressed from them. Upon further inquiry, it developed that every exacerbation of tonsillitis over the years was accompanied by a flare-up of his liver trouble. However, the patient paid little attention to this, not realizing that a connection might exist between the attacks of tonsillitis and his liver trouble. The temperature now and then was febrile. A few weeks prior to the time that the patient was seen he had had another attack of tonsillitis, which caused an exacerbation of his liver symptoms, and at this time he noticed that he was slightly jaundiced. The patient was very much concerned about his condition and was convinced that he was suffering from carcinoma of the liver. This suspicion seemed to be supported by the increased size of the liver, which he had noticed himself, and the rather painless development of slight jaundice of the sclerae. Despite treatment, he had lost 14 pounds in weight in the previous few months. His attending physician was worried about the recent developments and had suggested that he consult one of the authors. The patient was greatly relieved when the probability of a connection between his liver symptoms and a chronic focal infection, probably arising from the tonsils, was explained to him. On this basis a tonsillectomy was advised and performed with dramatic results. One month after discharge

from the hospital the patient returned for re-examination. At this time his general appearance was quite different from that prior to operation. His appetite was good, he was able to tolerate any kind of food without distress and in three weeks he had gained 4½ pounds in weight. All signs of jaundice had disappeared. At this time the liver was only slightly increased in size. The patient stated that he had not felt so well in years and that this was the first time he was completely free of liver symptoms, and was able to eat all kinds of food and enjoy his meals.

In some cases an intimate association between hepatic lymphangitis and appendicitis (lymphangitic form) can clearly be established. In these cases the appendix, in a way, acts as a primary focus, and its removal produces rapid improvement of the liver pathology. Similar cases have been reported by other authors. A case described by Saathoff is worthy of note:

The patient, a boy of 5 years (in this case the age of the patient should be borne in mind), suffered recurrent attacks of acute appendicitis, each attack accompanied by enlargement of the liver, bilirubinuria and almost acholic stools. In this case the appendix was removed and all liver symptoms subsided completely following its removal.

What is the subsequent course of lymphangitis hepatica? Certain damage to the liver cells may occur in the very beginning, as shown by intolerance for food, increased urobilinuria, etc. This liver cell damage increases with the frequency of the liver attacks and the toxic influence of the focal infection. Attacks of hepatic jaundice lasting several weeks can be observed. The enlargement of the liver becomes permanent and its consistency becomes harder. As in all forms of hepatitis lasting over a long period, while the same toxic cause persists, cell degeneration and cell necrosis go parallel with an increase of fibrous tissue.

Cirrhosis may be the end-stage of this form of infectious toxic hepatitis where, in some cases, the relation to a focal infection is well illustrated in the history, as in the following interesting case report:[1]

The patient, a white male, age 30, a physician, gave a history of a "weak liver" in youth, and this was confirmed by repeated glucose tolerance tests. In 1939 he had typhoid fever, followed by slight jaundice, which persisted for over four months following subsidence of the typhoid infection. The serum bilirubin was 3.6 mg. There was a history of lowered tolerance for food, especially fats, which was persistent. In October, 1939, he felt well and was able to resume his practice.

In June, 1940, gastrointestinal and liver trouble reappeared. The patient stated he felt as though he were "blown up". At this time he noticed that with each recurrent attack of tonsillitis there was a marked accentuation of his liver symptoms. Neurocerebral syndromes appeared, manifested by tremor of the hands, slowing down of all voluntary movement and difficulty in finding the right words to express himself. Signs of a disturbing amnesia appeared. The blood Wassermann was negative. Slight jaundice was again observed during the course of an attack of acute tonsillitis. The serum bilirubin rose to 1.7 mg. The sedimentation rate was accelerated. Eye symptoms, consisting of dimness of vision and

diplopia, were observed. All symptoms deteriorated with constipation. On examination by an opthalmologist it was found that there was a spasm of the retinal vessels. The patient maintained that he could voluntarily bring about deterioration of all symptoms through constipation. The symptoms, with changing states of mild jaundice and periods of deterioration of the neurological symptoms, dragged on through the year 1942. The white blood cell count was found to be 12,000 with 12 per cent of eosinophiles. The blood pressure was 135/80. No parasites were found in the stool. The Widal liver test was positive. After the intake of milk, the leucocytes dropped from 5,000 to 4,000. The attacks of acute tonsillitis became more frequent and were paralleled by regular deterioration of syndromes of hepatitis and neurological signs. It was noted that there was a lack of concentration and difficulty in speaking. Orientation became difficult. The patient was unable to find the door in his own surroundings when trying to leave the room. There was no enlargement of the liver and no ascites was demonstrable. Tonsillectomy was advised, but postponed until February 4, 1943, when it was performed under local anesthesia. The operation was uneventful, but following it the patient gradually passed into hepatic coma and he died two days postoperatively. Autopsy disclosed the liver to be about half the normal size and showed evidence of advanced cirrhosis. No pathology of significance was found in the other organs. The brain was not examined because of lack of consent.

Summary

The clinical symptomatology of this interesting case is very complex. The nervous syndromes associated with long lasting liver damage are entirely different from those due to lenticular lesions as observed in Wilson's disease. However a common denominator for the simultaneous damage to the liver and the central nervous system was given in the careful self-observation of this Doctor-Patient who clearly described the relation of any exacerbation of his syndromes to the flare up of a chronic tonsillitis as a focal infection.

The authors feel that this case verifies and well illustrates the hypothesis that focal infections in lymphatic tissues in various parts of the body may be the exciting factor in the production of a hepatitis, which has been designated as lymphatic hepatitis (lymphangitis hepatica) and which may lead in the end to a toxic cirrhosis.

(To be continued)

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BLOOD TEST FOR CANCER*

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The ideal criteria for a diagnostic test should include the following:

1. The results should be reproducible.
2. The reaction should be specific, that is
   a. it should not occur in normal individuals or in patients with other diseases than the specific disease tested for and
   b. it should occur in all cases of the specific disease.

If, in addition, one could perform such technics easily and economically, nothing would be lacking for a perfect test. Unfortunately, at the present time, no procedure employed in medical diagnostics meets these criteria absolutely and this deficiency is certainly lacking in cancer diagnostics. However, it is possible to make use of technics which may lack absolute specificity if the limitations inherent in their application is known.

Although there have been numerous attempts to develop diagnostic blood tests for cancer these efforts have not met with any lasting favor. The pessimistic outlook which has prevailed is epitomized by Willis[13] who states "The hope that biochemical studies of the cancerous patient will reveal anything fundamental regarding the nature or growth of cancers or will lead to diagnostically useful tests, has so far proved a vain one, and is likely to remain so."

While it has not been my experience that the findings to be reported are absolutely specific for malignant neoplasia, I shall attempt to indicate that significant alterations in the plasma reducing power and heat sensitivity occurs in the cancer host, and that these changes can provide an aid in the diagnosis and follow-up of cancer cases. In addition, I shall summarize some of the experimental observations aimed at elucidating the underlying mechanisms involved and their implications concerning systemic alterations in the protein metabolism of cancer patients.

In 1944 Savignac et al[11] reported on a decreased ability of serum of cancer patients to reduce methylene blue as compared to normal individuals and patients with many non-neoplastic conditions. Using a modification of Savignac's technic I was able to confirm his findings and in published reports indicated that such alterations were found in approximately 75 per cent of cancer cases of diverse types[1,2]. Similar findings were also obtained by Morris using my procedure at the Methodist Hospital[9]. In addition, Huggins[8], employing the reduction of triphenyl tetrazolium chloride as a measure of serum reducing power, substantiated the decrease in the reducing power of the serum of cancer patients. In the procedure to be evaluated the reducing power is measured by the ability of a plasma sample to decol-

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orize a standard amount of methylene blue, the determination being performed as follows:

1. Place 1 cc. of plasma (or serum) into a Wassermann tube.

2. Add 0.2 cc. of specially standardized methylene blue solution (0.15 per cent in distilled water).

3. After mixing, immerse tube in a vigorously boiling water bath (a drop of capryl alcohol may be added to prevent frothing).

4. Observe time for the complete disappearance of the blue color.

In a study of more than 1,000 plasma samples from presumably healthy individuals, a characteristic distribution curve was obtained, the peak of which lay between 8 and 8.5 minutes. The upper limit of the curve was found at 10.0 minutes. This is at variance with similar studies of plasma samples from individuals with a wide variety of malignant disease. Here the reducing time values were more prolonged and in some cases required more than 20 minutes to bring about complete reduction of the dye. This may be seen by the percentage of cases having reducing time values of 11 minutes or more, viz., carcinoma of the breast 40 per cent; carcinoma of the lung 73 per cent; carcinoma of the cervix 59 per cent; carcinoma of the colon 68 per cent.

The mechanism of this change in reducing power in association with the presence of malignant neoplasia appears to be part of a systemic effect on protein metabolism. The previous studies by Sagignac et al appeared to implicate the albumin fraction as the principal plasma component responsible for the reduction of the dye. My studies suggest that the -SH group of a protein component of the plasma, most probably albumin, is responsible for the reducing power as measured by the technic described.

In an attempt to evaluate the relation of the sulfhydryl groups and the reduction of methylene blue, a study was undertaken with various compounds of known -SH and -S-S- structures[3]. Glutathione, cysteine hydrochloride, and methionine were made up in equimolar solutions (0.0325 M) in distilled water. One cc. of the glutathione solution was added to 0.2 cc. of 0.13 per cent methylene blue solution. In a similar manner, the dye was added to 1 cc. samples of the cysteine and methionine solutions. The tubes were then immersed in a boiling water bath and observed for time of complete decolorization. The tube containing methionine and methylene blue failed to show any change in color in spite of continued boiling for one and a half hours. On the other hand, complete decolorization was noted in the tubes containing cysteine HCl and glutathione in 6.0 and 15 minutes respectively. The reduction of methylene blue by cysteine and glutathione and not by methionine is an indication that in these compounds at least a free -SH bond is required. The more prolonged time for glutathione (15 minutes) as compared with cysteine HCl (6 minutes) would seem to indicate that the availability or reactivity of the -SH bond may be altered by its location in the molecule. Thus, in the cysteine the -SH is terminal and presumably unhindered in its activity. In the case of glu-

tathione, the internal location of the -SH bond seems to decrease its reactivity. The reversible decrease in the reducing power of plasma associated with malignant neoplastic disease might be explained on the basis of changes in the spatial configuration of the albumin molecule. Such changes would be readily reversible and would not necessitate changes in the amount of total proteins or -SH bonds. This is of importance since the observed decrease in reducing power is not correlated with changes in the concentration of the plasma proteins within rather wide limits. Thus it appears that the reduction of methylene blue by plasma in the technic described is a measure of the reactivity or appearance of the reducing groups rather than a measure of the total number of such groups potentially available[4,5,12]. This suggestion that malignant neoplasia induces a qualitative variation in the albumin molecule of the host is also supported by the studies of Huggins[8] on the thermal coagulation of serum from control and cancerous individuals.

While the presence of malignant disease is associated with a deficiency in albumin fabrication as evidenced by a lowering of the reducing power and often times a lowering of the serum albumin, the fibrinogen concentration tends to undergo elevation. This finding, reported by various investigators and corroborated in our own studies, indicates that the various protein components of the plasma are influenced differently by the presence of malignant disease[6].

When plasma samples from individuals with and without malignant disease were exposed to a standard amount of heat, it was noted that the former group tended to show a greater degree of turbidity[6]. The procedure employed is as follows: (1) 1 c.c. of plasma is placed in a Klett colorimeter tube and diluted to the 5 c.c. mark; (2) a reading of the light transmission is taken in the colorimeter; (3) the tube is immersed in a boiling water bath for exactly 10 seconds; (4) after cooling and drying the tube, a second reading of the light transmission is taken.

The difference between the first and second readings is a measure of the coagulation or turbidity produced and has been termed the coagulation value. When the values of plasma samples from healthy individuals were plotted, a peak was found at a value of 48, while less than 1 per cent of the cases extend beyond 80.

This was quite at variance with the results obtained when plasma samples of cancer patients were tested, since more than 60 per cent of the cases were found to have coagulation values of 80 or above. In view of the small percentage of controls with coagulation values above 79, it was arbitrarily decided to adopt a coagulation value of 80 or above as suggestive of the presence of malignant neoplasia. In a series of 199 cases of diverse cancer types, the mean of the coagulation values was 99.

It should be emphasized that the coagulation values obtained will vary when different colorimeters are used. Therefore, it is necessary for each laboratory to establish the normal limits for its own machine. When this is done, the values obtained with the plasma of cancer patients will show the same type of variation as reported here.

Chemical investigation of the basis of these changes indicated that they are related to the fibrinogen concentration. Similar heating of serum samples failed to induce a turbidity, and parallel determinations of fibrinogen and coagulation values revealed a correlation between the two. Since individual cases were encountered wherein the fibrinogen concentrations were the same but wide divergencies were noted in the coagulation values, it would appear that some other factor or factors are involved in addition to the fibrinogen concentration.

The clinical application of these technics to cancer diagnosis is based on the observations that the plasma reducing power and heat coagulation values of healthy individuals fall within certain well definable limits whereas similar determinations performed on cancer patients yield values outside these limits in the majority of cases. These observations are valid over the ages from childhood to old age. It has therefore been assumed that the elevation of either or both of these values above normal limits represents a systemic abnormality suggestive of the presence of malignant neoplasia.

In the course of clinical application of these procedures the following technical precautions have been defined:

1. Blood samples should be drawn from subjects in the postabsorptive state and the patient should be drug free. (We have found that penicillin, streptomycin and pyribenzamine induce false elevations of both the reducing time and heat coagulation values).

2. Adequate amounts of dry sodium oxalate should be used as the anticoagulant.

3. Determinations should be performed as soon as possible after withdrawal of the blood. If not performed immediately the plasma should be separated by centrifugation and the plasma removed and stored in the refrigerator for not longer than twenty-four hours.

4. While the technics are simple, adequate experience should be obtained by determinations performed on known control and malignant samples until results are reproducible.

The application of these criteria have been applied in the clinical cases to be reported. These data represent a compilation of the results of three independent groups of investigators aimed at testing the efficacy of using the plasma methylene blue reducing time and heat coagulation as a diagnostic aid in the identification of malignant neoplasia[7]. With few exceptions plasma testing was performed without knowledge of the clinical diagnosis and in almost all cases the diagnosis of cancer cases was confirmed by biopsy.

The principal investigators and institutions concerned are as follows: Maurice M. Black and Israel S. Kleiner, Departments of Pathology and Biochemistry, New York Medical College; Frank L. Pollack, Fort Jay Station Hospital; Max M. Stettner, H. Baron and B. W. Lowenstein, Department of Biochemistry, New York Medical College[12].

When the aforementioned criteria were applied to cases of malignant neoplastic diseases it was found that a positive value was obtained in 416 of 468 cases tested, or an overall identification accuracy of 89 per cent. The findings listed in Table I will illustrate the results in the more common forms of malignancy.

It should also be pointed out at this time that a definite correlation was found to exist between the efficacy of a therapeutic procedure and the plasma reducing time and heat coagulation values. Complete surgical extirpation of a carcinoma will be followed by a return of the elevated plasma values to normal within a period of 7 to 10 days. Although small foci of malignant tissue may conceivably persist after a return of the blood values to normal, the failure of such a return

TABLE I

DIAGNOSIS OF CANCER CASES BY THE USE OF THE METHYLENE BLUE REDUCING POWER AND HEAT COAGULATION TECHNIC

Site	No. Cases	No. Positive	% Accuracy
Breast	67	56	84
Bladder	12	11	92
Cervix	38	32	84
Colon	30	29	97
Esophagus	10	9	90
Hodgkins	11	10	91
Larynx	10	9	90
Lung	30	29	97
Mouth(incl. tongue and nasopharynx)	30	29	97
Ovary	19	18	95
Prostate	32	29	91
Rectum	28	28	100
Sarcoma	13	13	100
Stomach	26	24	92

following a therapeutic procedure is extremely strong evidence that the malignancy has not been eradicated.

I should also like to emphasize that these reactions are not based on the presence of cachexia or a long standing debilitating process. Approximately one-half of the cancer cases tested were ambulatory and pursuing normal activity, and it has been our experience that the plasma changes described here may occur with lesions which are minimal in size. Among such small lesions have been: osteogenic sarcoma of the tibia, 3-4 cm. in diameter; gastric carcinoma, 1-2 cm. in diameter; choroid melanoma, less than 1 cm. in diameter and a cervical and laryngeal carcinoma which showed blood alterations 4 months to one year before clinical mani-

festations of the lesions, as well as others. Further, it has been observed that marked involvement of the liver by tumor metastases may be associated with a reversal of a positive to a negative reaction.

In testing a large series of widely diverse forms of non-neoplastic diseases we have found that cirrhosis, pregnancy, acute rheumatic fever and tuberculosis could not be adequately differentiated from the results obtained in the cancer group. Excluding these conditions, however, 91 per cent of 558 cases of diverse forms of non-neoplastic diseases yielded normal values with both the reducing power and coagulation technics.

Similar results were also obtained in testing a series of 116 cases of nonmalignant neoplasia wherein 92 per cent of the cases yielded values within the normal range with both technics.

The results obtained in this series of 2,119 individuals tested by both technics are summarized in Table II. In reviewing these data it will be evident that the procedures described do not completely fulfill the criteria mentioned above as

TABLE II
SUMMARY OF DIAGNOSTIC ACCURACY

Group	M.B.T. No.	M.B.T. % Accuracy	Coagulation No.	Coagulation % Accuracy	Comb. Technics No.	Comb. Technics % Accuracy
Control	1366	99	977	99	977	99
Malignant Neoplasia	931	57	473	66	468	89
Non-Neoplastic Disease*	791	97	558	91	558	91
Non-Malignant Neoplasia	116	99	116	92	116	92

*Excluding tuberculosis, rheumatic fever, cirrhosis and pregnancy.

those of an ideal diagnostic test. While they are readily reproducible, technically simple and economical, they are not absolutely specific nor do they detect 100 per cent of cancer cases. From a practical standpoint, however, the accuracy, simplicity and economy of performance are sufficient to warrant the employment of these procedures as a screening device in mass survey examination for cancer.

In summary, the following conclusions appear justified:

1. The presence of malignant neoplasia induces changes in the reducing power and the heat coagulation of the plasma of the host in a high percentage of the cases tested.

2. These reactions are not based on changes coincident to cachexia.

3. The reactions are not entirely specific as cirrhosis, pregnancy, acute rheumatic fever and tuberculosis tend to induce similar changes.

4. Within the limits indicated the use of these technics in the manner described provides an aid in the detection and follow-up of malignant neoplastic disease.

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CORTICODIENCEPHALIC GASTROINTESTINAL SYNDROMES IN EPILEPTICS*

(PART VI)

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New York, N. Y.

TROPHIC PHENOMENA—ANATOMICAL LOCALIZATION

Before concentrating our attention upon the work of Archambault and Fromm we should remind the reader that trophic functions are related to metabolic function. The growth of the body is a very important endocrinologic problem. There are many diseases of the glands of internal secretion which cause disturbances in the growth of not only the musculoskeletal system (but also of other systems such as the cardiovascular, etc. The neurogenic control of such problems of growth lies in the hypothalamic, tuberal and mammillary region among other portions of the mammillothalamic system. We have previously referred to the mammillary body as being large in animals of huge body size. At this point we cannot again refer elaborately to the literature even on this matter alone although it has momentous significance. Neither can we elaborate further on the mammillothalamic system in relation to growth. We leave it to the reader to investigate further the field which we have mentioned above, that is, the cardiovascular and endocrine system in relation to the mammillothalamic tract and the problem of growth. Secretory functions, whether of the salivary glands or those of the intestinal and stomach glands, have a common neurogenic central control. The glands of the pancreas and liver also fall into the same category. Pavlov and his workers realized this. That is why they included in their experiments the endocrine gland system and effects upon it of auditory stimuli. Glandular and trophic phenomena, having such a wide neuroanatomic substratum, are so important that any data elucidating their neurogenic control is of utmost significance whether it comes from the laboratory, clinic or operating room. We will therefore leave the mammillothalamic system completely alone and begin a review of the final common pathway.

In regard to the final common pathway, that is its sensory component and motor component, it is important that before we touch upon the work of Archambault and Fromm on muscular atrophy in relation to this system and its autonomic component, we mention some of the facts regarding this system that Spiegel outlined in 1932 during his experimental work with the centers of the vegetative nervous system.

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Spiegel showed for instance that there are two groups of systems in the spinal cord that conduct painful stimuli from the viscera. One is composed of long neurones and another of short ones. The first group joins the old tractus spinothalamicus. The crossed and uncrossed spinothalamic tract conducts painful impulses from the arteries of the leg. After elaborating at length on the somatic afferent nerve that conducts visceral pain and referring to a great many authorities to whom we have already referred in other connections, Spiegel discusses centripetal impulses within the spinal cord in the pathway that conducts them from the viscera.

Spiegel was however very emphatic when he stated that the knowledge of centrifugal and centripetal relationship with regard to pain conduction to the higher centers from the viscera was practically nil. He even analyzed some paths of the autonomic with regard to respiration. He showed that stimulation of the afferent end of the splanchnic changes the respiration in decerebrate animals. He stated that evidently there is some connection between these afferent pathways and the center of respiration, but nothing is known of their intimate relation either to the thalamus or the cerebral cortex. Before beginning our reference to the purely clinical data of Archambault and Fromm it might be relevant to stress that an investigator of the calibre of Spiegel did not hesitate in the least to utilize experimental data on lower forms when such an important subject as the neurogenic control of gastrointestinal function was involved. There are a great many references to the literature in the paper by Spiegel, particularly with regard to afferent and efferent conduction of impulses with relation to the spinal cord and the viscera most of which are clinical.

Spiegel also stated that the centrifugal pathways of the vegetative nervous system are more easily determined than the centripetal. He remarked that there is little agreement concerning the cortical representation of internal organs. The largest part of his references deal mostly with the pyramidal tract and other tracts in the final common pathway. He refers particularly to Bechterev the way we did and to some of the other authors to whom Watts and Fulton referred. This we can see from some of his additional remarks. He stated: "If one studies the representation within the cortex from which the internal organs can be stimulated it is found that the majority of such foci are located within the motor area or its vicinity. This is especially true for the organs controlling smooth muscles (intestine, pelvic, viscera, blood vessels, sweat glands and salivary glands). Cortical centers which innervate skeletal muscles have a close topographical relation in visceral organs such as the urinary bladder, etc." One will note a striking difference between pure clinicians such as Archambault and Fromm and experimentalists such as Spiegel. The former chose the subject of atrophy and scoured the seven seas of neurology to arrive at one anatomical conclusion. Spiegel and others were not satisfied with the trophic but investigated the sensory and secretory phases as well. In our limited concept of laboratory anatomical work we have however one criticism to offer and that deals with somatotopic localization. Most experimenters

fail to stress this point. In neurology we find it of utmost importance to differentiate between a lesion that affects the upper extremity and one that involves the lower. We fail however to stress the anatomical differences between lesions that affect the esophagus and rectum. Spiegel referred to a great many authorities who localized the centers of skeletal muscles within the cerebral cortex near those of the viscera mentioned above. He concentrated also on trophic centers. Figures 30 and 33 may be compared with the above and quotations of next paragraph.

The more we refer to the work of this authority the more we feel guilty as we previously affirmed, of the fact that in concentrating upon the mammillothalamic tract, we omitted to impress the reader with the fact that the final common pathway also contains a tract or a number of fibres which control visceral functions just as the mammillothalamic. Another important reference which Spiegel made is:

Fig. 39

"salivation in epileptic attacks is produced by injury near the ventral part of the gyrus centralis anterior." "Pupillary reactions associated with eyes turning in epileptic patients point to various cortical vegetative centers." From this we can see that we were not the only ones to relate certain epileptic phenomena with such areas. In referring to the final common pathway Spiegel stated that a corticofugal pathway for the vegetative organs happens to be closely related to the position of the pyramidal tract. He referred to the fact that contraction of the bladder has been localized in the lateral column (Spiegel and McPherson 1925) and not in the posterior column as thought by L. R. Müller. It is evident that Spiegel would not have taken issue with Müller had he elaborated more than he did on the lateral nucleus of the thalamus. This structure of the dorsal thalamus and its immediate vicinity seems to carry not only pain and temperature but also vibratory stimuli

and contains fibres of the rubrothalamic tract. It is also connected with the olfactovisceral portions of the thalamus. The literature furthermore suspects the lemnisci systems to end in almost every portion of the optic thalamus. The only reference to the pathways which are not situated within the pyramidal system is the following from Spiegel: "the pyramidal tract, however, does not seem to be the only way by which the centrifugal impulses can reach the internal organs. Cortical impulses may reach the hypothalamic centers by way of fibres from the frontal lobe to the globus pallidus, or to the thalamus, that is, we have to distinguish a pyramidal part and also an extrapyramidal part of the centrifugal vegetative tract." If there is anything emphatic about the work of Spiegel and his associates it is that throughout the entire paper there is no reference whatsoever to the mammillothalamic system. All these authorities adhered closely to the final common pathway, either the pyramidal or extrapyramidal. Previously we dwelt upon the autonomic in general. In the following work of Archambault we merely discuss muscular atrophy and its autonomic control.

Far be it from us to attempt to champion the cause of the final common pathway adherents. We feel this school can stand on the record of such a man as Bechterev alone. Furthermore, the references given by Spiegel contain the name of such an outstanding authority as Schiff, whose work dates back almost a century. This, the pyramidal tract and final common pathway or even spinothalamic schools have among their proponents excellent laboratory investigators to whom the reader is referred through the paper by Spiegel. We have spent so much time on laboratory data dealing with the mammillothalamic tract that for us to devote more space to the experimental work on the final common pathway school, would be superfluous. Our choice has therefore been the data presented by Archambault and Fromm.

Before beginning presentation of their material we feel however that Archambault has made an extensive analysis of the pathway of the autonomic and largely those pathways which extend not only from the spinal cord but also within the brain stem in relation to facial hemiatrophy. It is not his analysis which we are concerned with, it is rather the plight of the pyramidal and related systems in relation to the fibres of the autonomic. Although it is this system, particularly the part which deals with the spinothalamic portion and the fibres which end in the postcentral area that we feel has been done somewhat of an injustice. Any clinician with a minimum amount of neurological experience has at one time or another seen some syndromes of the brain stem with which have been connected manifestations of autonomic disturbances. The syndrome which is particularly associated with such manifestations is the basilar artery which is in one way or another affected by hemorrhagic or embolic or thrombotic lesions. In these cases we see various combinations of cranial nerve disturbances with contralateral paralysis or anesthesia. When such lesion occurs there is now and then a sweating or a hyperemia or some other manifestation of autonomic imbalance situated on the side of the lesion. We are sure that Archambault and the neurologists to whom he referred in his paper were very well aware of the fact that specific autonomic

tracts were involved in their cases. Yet no one mentioned the specific location of such tracts in the tegmentum or elsewhere and emphasized them.

The particular syndrome combinations in which there is usually a nuclear involvement of a cranial nerve associated with the contralateral paralysis or anesthesia are usually located in the pons or in the medulla oblongata. The syndrome of Avellis and its various combinations fall into this group. Usually the ninth and tenth nerves are associated with the contralateral paralysis or anesthesia. Tilney and Riley have devoted a great deal of space in their books to various combinations of such syndromes. In spite of their elaboration on the various syndrome combinations, the tracts laid down by them have not been elaborated upon as far as the autonomic nervous system is concerned. Neither have other neurologists of outstanding reputation devoted a great deal of space on the autonomic central nervous system in relation to the syndromes mentioned above. In the many cases

Fig. 40

of mesencephalic encephalitis that are seen daily in clinics there are noted any number of autonomic signs associated with unilateral tremor or rigidity. Everyone knows about the mesencephalon syndromes of Benedikt and Weber because these have been stressed as having specific motor and sensory features in combination with cranial nerve changes. The occurrence of bilateral vegetative disturbances such as sweating or hyperemia on both sides of the face and bilateral alopecia in combination with a unilateral rigidity is due to the multidecussational and commissural vegetative fibres that are located near the midline. For this reason the clinician has been perplexed to the extent of fearing to venture their segregation into syndrome groups. Thus the gastrointestinal vegetative centers also escaped emphasis. It is true that some have mentioned the various nuclei that might have autonomic functions particularly those which are connected with the parasympathetic nervous system.

Far be it from us to continue our emphasis upon the neglect of outstanding authorities to stress the autonomic nervous system in its relation to the final common pathway. We feel that neurology has had enough champions of extensive reputation on a clinical plane to be able to stand on its own merit particularly with the advances made in the past century. We wish to emphasize however that of all systems neglected in cerebral neurology, the one dealing with head and neck movement localization and the one concerned with the exact localization of autonomic function in the final common pathway have been the most neglected. We realize that there are many parts of the cerebrum which have been neglected. Kappers, Huber and Crosby have really pointed out that an area as large as the island of Reil has received very little attention from comparative neuroanatomists as contrasted with other portions of the cerebrum. Just as certain anatomical problems are left so are there clinical conditions which call for localization. The internist looks for the smallest petechiae to help him diagnose a bacteremia. The endocrinologist and dermatologist inspect, palpate and measure every change in the skin osseous system and glandular structure and utilize such findings along diagnostic and therapeutic lines. If the neurologist paid similar attention to the manifestations of central autonomic imbalance in the areas scrutinized by the former and did not fear to classify them the neuroanatomist would have a better field to choose from in order to successfully group his observations. What has been said above applies likewise to the clinical observations of gastrointestinal and trophic muscular phenomena. We shall see how Archambault and Fromm attacked this problem. The problem of the acceptance of the spinothalamic and the pyramidal tract as containing fibres subserving autonomic functions is however of the utmost importance. There is not only clinical but extensive experimental material to be taken advantage of by the clinical neurologist. Yet everyone seems to have failed to answer that call. They have answered it in syndromes of the mesencephalon and of other portions of the brain stem. But above those areas no worthwhile attempts have been made and stressed in textbooks on neurology.

Since Spiegel elaborated at length with regard to centrifugal and centripetal fibres in relation to the autonomic control from the cerebrum to the viscera, we could if we chose, follow that scheme and discuss various disease groups that fall into these systems. Among the spinothalamic tract diseases we could mention syringomyelia and emphasize various autonomic conditions that might be classed with this syndrome, particularly the muscular atrophy that is seen in such diseases. For the pyramidal pathway we could also select a disease such as amyotrophic lateral sclerosis. In this condition, as is commonly known, there is a definite selective type of muscular wasting associated with evidences of irritation of the pyramidal tract. Many authorities have connected degeneration of the fibres involved in this pyramidal tract system with associated degenerated changes in the frontal lobe in cases of amyotrophic lateral sclerosis. Whether such degenerative changes indicate involvement of the autonomic pathways that are responsible for the associated muscular atrophy has not been definitely determined. In this

way we could accumulate a great deal of clinical data and refer to a great many papers and texts on this subject. All that material would however be largely clinical without definite anatomical lesions to point to definite tracts within the cerebrum subserving sympathetic or parasympathetic functions. Suffice it to say therefore that almost all the clinical data presented everywhere is valueless because the neurologist who dealt with the subject failed to be as specific as they were with the localization of such symptoms as paralysis of one side of the body or anesthesia of one side or of one extremity. In other words while every worker clinically or otherwise has busied himself in the last century with the establishment of definite pathways subserving visual, auditory, tactile, motor or other functions, he has nevertheless invariably failed when it came to the definite localization of the autonomic disturbances in specific tracts within the cerebral hemisphere.

Rather than elaborate further and refer to various other papers on the subject of centrifugal and centripetal components of the autonomic along the final common pathway, we felt that a direct lengthy quotation from the work of Archambault and Fromm would more than elucidate the problems involved in the subject of trophic tracts in the central nervous system. Although we have now and then resorted to direct quotations from the viewpoint of emphasis and for the purpose of the presentation of the exact data, none of our direct quotations presented the entire problem of the subject under consideration as the following (Archambault and Fromm 1932 pp. 573 to 576 inclusive): "How shall we explain the occurrence of complete unilateral atrophy or so-called total hemiatrophy? The answer has already been given by Brissaud (1899) and his pupils Calmette and Pages (1903), but has never received serious consideration. This brings us to the theory known as the cephalic trophoneurosis theory. Brissaud, having in mind the total or crossed hemiatrophy observed by Henschen, Marie and Marinesco, Lunz, Raymond and Sicard and others, regarded facial hemiatrophy as only a partial or segmental type of his trophoneurose centralic and predicated a lesion of the periependymal gray matter of the Sylvian aqueduct and oral portions of the fourth ventricle, being strengthened in his belief by the occasional occurrence of facial hemiatrophy in connection with syringomyelia." (Here it might be well to remind the reader of the mammillothalamic system. Whenever we referred to this system we invariably felt that we were slighting some other tracts that would carry autonomic fibres just as well as the mammillothalamic. We have in mind the fibres of the preoptic components of the striæ medullaris and the fibre tracts of the dorsal longitudinal fasciculus the last mentioned being strictly of periventricular origin. The literature on this was probably undeveloped in Brissaud's time otherwise he would have stressed this tract). "Not only is this conception perfectly logical, but a number of cases mentioned in the present paper apparently confirmed Brissaud's interprétation. In fact, a large number of facial hemiatrophy cases reported especially in recent years have been attributed, some of them without rhyme or reason, to lesions of the diencephalic floor, lateral wall of the third

ventricle or periependymal gray matter of the Sylvian aqueduct. In other words, Brissaud's hypothesis has found considerable favor, but it is believed that the pendulum now has swung too freely in the opposite direction and we think that Brissaud's theory applies essentially to cases of total hemiatrophy for which there surely exists no more plausible explanation. A case in point is that reported recently by Vivoldo (1928 and 1929), and an instance of total hemiatrophy which, inadvertently, we failed to mention when discussing this particular group.

"A man, age 28, presented a striking left facial hemiatrophy with plaques of canities. The left half of the thorax and the left extremity likewise exhibited definite though less pronounced atrophy. Painful and spasmodic phenomena were present throughout the atrophied regions. A syphilitic etiology was evidently concerned.

"Vivoldo's observation is strongly suggestive of a lesion of the right hypothalamus encroaching on the ventral nuclei of the thalamus and giving rise to

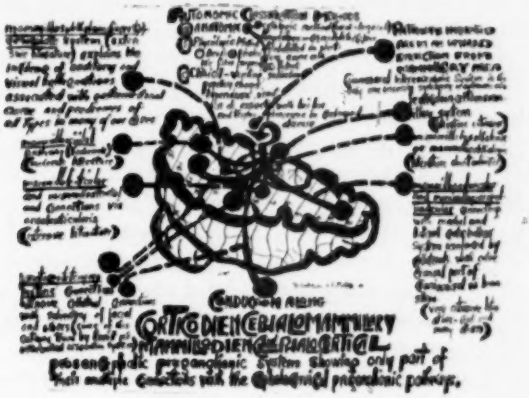

Fig. 41

so-called central pain. That the more common facial hemiatrophy likewise may depend on a lesion of the ependymal region of the mesencephalon or metencephalon seems certain in a few cases. (The cases of Langelaan, 1913; Kirschenberg, 1926; Krueger, 1916, and Leri, 1926). But such cases are exceptional and it is difficult to conceive that lesions at a higher level can give rise to facial hemiatrophy as Wartenberg and others have assumed. This naturally hinges on the ignorance concerning the level at which the cervical sympathetic fibres become detached from the contingents destined for the trunk and lower extremity." (Throughout the foregoing and in the following we will note that Archambault and Fromm successfully took clinicians to task in regard to their views on clinical grounds. What we fail to understand is why these authorities neglected so much of the clinical and anatomic literature pointing towards the diencephalon. If the reader checks back on our data on water metabolism alone and upon its chronology he

will note data which these investigators might have ably handled they neglected. In Figure 39 we show how trophic centers are related to neurogenic gastrointestinal centers.)

"Wartenberg has suggested the possibility that a somatopic subdivision of the trophic centers in the diencephalon may exist and, in order to account for the fact that in hemiatrophies the face is involved with such predominant frequency, he has invoked the principle of phylogenesis and ontogenesis, calling attention to the relative inactivity of the craniofacial segment as compared with the trunk and extremities during the development period of life. The latter assumption is not easy to reconcile with the fact already emphasized that facial hemiatrophy, in a considerable number of cases, has developed in middle and even in late life.

"The next factor that requires an explanation is whether one is warranted in assuming that trophic cell groups and fibres actually exist and, if so, that they belong to the sympathetic system. That nutrition and growth of the body tissues depend on both blood supply and neurogenic influences hardly needs mention. The trophic influence of the central nervous system has long been recognized. The trophic control of the somatic musculature by the ganglion cell complexes giving origin to the cranial and spinal nerves is today universally admitted and well illustrated by acute anterior poliomyelitis, amyotrophic lateral sclerosis and other diseases. In acute anterior poliomyelitis there is a diffusely infiltrating inflammatory process involving not only the anterior horns but the lateral and posterior horns and even the white columns, and clinically there is more than muscular atrophy, namely, atrophy of the bones and vasculature, anomalies of the subcutaneous tissue (adiposity, trophedema), vasomotor and secretory disturbances, visceral ptosis, etc. While we are well aware that changes in the bones in part may be explained by functional inactivity (hysterical paralysis, surgical immobilization), as was amply demonstrated during the recent war, we do not believe that this factor alone suffices and we have seen cases of poliomyelitis progressing to substantial recovery within a few weeks or months in which roentgenograms revealed definite skeletal changes in the affected limb. We likewise have seen two cases of hysterical paralysis of several years' duration presenting definite asymmetry of vasomotor and secretory function but in which careful measurements did not reveal material differences between the two sides as regards either the length or the circumference of the affected limb or limbs." (We are rather surprised that Archambault and Fromm omitted, even though the literature did, the cerebellum and its pathways. The existence of cerebellotectal and reticulocerebellar pathways suggests that muscular atrophy might occur in patients with chronic cerebellar disease. One of us, Patterson and Weingrow 1937, presented a case of epilepsy showing such a syndrome. Crossed and uncrossed types of cerebellar disease has been studied by us in our epileptics, some cases being verified by pneumoencephalograms.)

"One of these cases was that a woman, aged 23, who had been permitted to display a classic left hysterical hemiplegia since the age of 12.

"The other case was that of a girl, aged 16, examined at a local hospital, who exhibited a complete spastic monoplegia of the right lower extremity which developed at the age of 8 years within a few days after a railway collision in which an older sister was killed.

"The hemiatrophy occurring in connection with infantile hemiplegias already has been mentioned, and it is interesting to note that in the large and heterogeneous group formerly designated as the 'cerebral palsies of childhood', there are many instances of hemiathetosis in which the same stunting of growth of the affected extremities is observed as in frankly paralytic cases. We have the records of 3 cases of this kind exhibiting decided shortening and circumferential reduction despite the almost incessant overactivity of the corresponding musculature. It is well known that actual hypertrophy of the muscles is not rare in athetosis. Such observations clearly establish that some other factor, in addition to functional inactivity, is responsible for the atrophies encountered both in spinal and in cerebral lesions.

"Returning to the trophic disturbances occurring in acute poliomyelitis, it should appear entirely reasonable to maintain that the various atrophies, other than the muscular, depend on involvement of the motor ganglion cells but of entirely separate cell groups of fibre pathways, and one must instinctively think of the lateral horn and the tractus intermediolateralis." (For over a decade we have emphasized the finding of muscular, osseous, and cartilaginous residual atrophies in epileptics. We have in our writings presented evidence of the existence of the Brissaud-Vivoldo syndromes in many cases. We have also shown numerous instances of corticodiencephalic, muscular, osseous, chondral, dermal, mammary and testicular, etc., etc., hemiatrophy. "In certain diseases, likewise affecting the ventral horn cells but of purely degenerative nature, such as amyotrophic lateral sclerosis and so-called subacute or chronic poliomyelitis (for which term we would like to substitute that of progressive degenerative poliomyelopathy), we observe a strictly elective and progressive wasting of one muscle group after another. The occurrence of pains of causalgic type and vasomotor crises either resembling Raynaud's syndrome or assuming a reversed physiognomy has been described very well by van Bogaert, but to the best of our knowledge no one has yet recorded atrophy of the skin, subcutaneous fat or bony structures in connection with amyotrophic lateral sclerosis or chronic poliomyelitis. It might be objected that these diseases appear much later in life than either acute poliomyelitis or facial hemiatrophy, but it is now well known that acute poliomyelitis no longer is an exclusively 'infantile paralysis' and it has been reiterated here that facial hemiatrophy may develop at any age.

"In a series of brilliant publications, L. R. Müller and his pupils, Goering and Böwing, assembled an imposing array of documents and discussed in minute detail the whole problem of trophism in an attempt to reach a truly scientific conclusion regarding the role played by the vegetative system and more particularly by its sympathetic division." (Here we must again remind the reader that we

regret that Archambault and Fromm did not specify the exact diencephalic tracts which Müller and his pupils had in mind in referring to the ventricular region as they previously did. Did they favor the fibres of the preoptic component of the striæ medullaris, the mammillothalamic pathways, the fibres of the dorsal longitudinal fasciculus or some system leading from the hypothalamus into the dorsal thalamus?) "Müller concluded that it is the sympathetic that is concerned with this function and that the trophic fibres course in part with the peripheral sensory nerve fibres and in part with the fibres accompanying the vascular apparatus. Goering, after referring to the view held by many authors that the trophic influences of the sympathetic system exert themselves through the medium of the vasomotor fibres, shrewdly remarked that the occurrence of facial hemiatrophy without vasomotor disturbances and, conversely, the occurrence of sympathetic

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RELATED TO EXCLUSIVELY CEREBRAL CONTROL
IN EPILEPTIC CASES is responsible for our
neglect of Correlation upon the
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Stimulation
PRECANGLIONIC
BRAINSTEM and
To Multilobar Autonomic Projection
of Cerebrum embracing midline Dorsal
fasciculus of Schütz) dorsal thalamus radiations
and the Spinothalamic pathways among others.

Fig. 42

disturbances including vasomotor symptoms without facial hemiatrophy show that the sympathetic, of necessity, must carry separate trophic fibre strands for the passive tissues of the face." (If Müller's theory is right then the dorsal longitudinal fasciculus of the periventricular system or even the mammillothalamic tract might be construed as carrying trophic function. The views of Müller are proved by modern experimentalists such as Stavraky and others who assign vascular control to the thalamus.) "Therefore, the absence of all other sympathetic disturbances in some cases of facial hemiatrophy is no argument against the sympathetic origin of the syndrome. Moreover, the fact that in many cases of facial hemiatrophy, definite signs are present which indicate a lesion or injury of the cervical sympathetic affords the best evidence that special trophic vegetative nerve fibres exist.

"The intimate mechanism presiding over the development of facial hemiatrophy is not easy to establish. Many authors who hold the vegetative system and particularly its sympathetic division, whether in its peripheral or its central course, responsible for the syndrome assume a state of more or less permanent irritability of the sympathetic. Wartenberg even went so far as to say that in facial hemiatrophy one may speak of *eine spastische Lämung der niederen trophischen Zentren mit gesteigerter reflektorischer Erregbarkeit* (a spastic paralysis of the lower trophic centers with increased reflex excitability). This view is based largely on the fact that until recently the trophic fibres were considered either identical with the vasomotor fibres or else as coursing exclusively with them in the periadventitial sheaths of the peripheral blood vessels. The occasional narrowing of the carotid and temporal arteries on the affected side in the cases of Bouveyron, Bergsohn and H. Wolff (mentioned in Marburg's monograph) undoubtedly had a share in promoting this interpretation. In the various observations briefly described in this paper both irritative and paralytic predominate by far, and, what is most important of all, practically in no case of facial hemiatrophy having sympathetic concomitants have the latter been exclusively of irritative or of paralytic type."

There has previously been presented data to show that the trophic fibres are independent of the vasomotor because the nuclear atrophy occurred independent of vasomotor phenomena in a number of patients. Both the trophic and vasomotor functions are neurogenically part of the autonomic system in the diencephalon and above this structure neurogenic gastrointestinal phenomena of an autonomic nature should therefore not be too distantly situated from the tracts subserving the other two functions. See Figure 39 for the neuroanatomy.

A detailed analysis of the material presented in the above quotation shows that although here and there, there are references to the diencephalon, the periventricular gray and the fact that Wartenburg claimed that there is a somatotopic localization within the diencephalon for trophic functions, most of the data presented in the paper by Archambault and Fromm points however towards the tendency to favor the localization of trophic fibres within the final common pathway, or the trigeminal part of the parasympathetic.

In the efferent alone and efferent afferent combinations as the Brissaud-Vivoldo syndrome we see, particularly, the repeated references by a great many authorities to the syndromes of pain in the affected side in thalamic lesions. This last is essentially of course a spinothalamic symptom. Moreover, throughout the paper by Archambault and Fromm there is extensive reference to the trigeminal nerve. In fact, besides a sympathetic theory there is a definite trigeminal theory for the conduction of trophic impulses. The trigeminal nerve as is commonly known has a great many pain syndromes among which may be mentioned all types of neuralgic headaches, as well as tic douloureux. In many cases of progressive facial hemiatrophy this syndrome of facial pain is mentioned as an accompaniment. The

trigeminal therefore forms part of the final common pathway combination with the spinothalamic and probably in both lemniscal systems. It also has a special path in the formation of the cerebellum.

This nerve is the oldest and most extensive of the cranial nerves. Facial pain, headache of gastrointestinal origin and encephalic neuralgias of pancreatic etiology and secondary to oral infection have all been attributed to the trigeminal nerve. It has a distinct lemniscal system which has been traced into the dorsal thalamus and into such of its parts that carry olfactovisceral functions. Its fibres stretch from above its nucleus in the pons towards the cerebral cortex paths along the various fibre tracts of the internal capsule. From below, in the nucleus of the pons, it extends downward into the cervical spinal cord and ends around the cells near the posterior horn within the substantia gelatinosa of Rolando at the level of the second cervical metamere.

The great many tracts to which this trigeminal complex within the brain and spinal cord connects may be seen by the very extensive references given to this subject by Kappers, Huber and Crosby. They described trigeminal tectal tracts in amphibians, birds, cyclostomes, plagiostomes and reptiles, as well as in teleosts. They also describe a trigeminomesencephalic tract in birds, ganoids and teleosts, reptiles and finally in mammals. In addition to the above they describe a trigeminal ventral cerebellar tract in birds, and reptiles. The phylogeny of this tract is also given. In addition to describing a dorsal trigeminal cerebellar tract, they devote a great deal of space to the trigeminocerebellar tract in mammals, and devote additional space to a description of the origin of this tract. In addition, space is devoted to the secondary ascending trigeminal tract in general, and particularly in mammals giving the avian homologues, the dorsal, the ventral, and finally giving details of the trigeminospinal tract in forms of animals such as described above. In clinical neurology we find few disease syndromes in which this nerve or its pathways are unaffected. It is here that it seems more important than the vagus or possibly any other cranial nerve. In experimental neurophysiology it also maintains a prominent place since its functions embrace many spheres from head-turning to mastication. Both in the reports of Davison and Goodhart as well as in Muskens we find the nuclei of the trigeminal associated in one parasympathetic chain with the nuclei of the 3rd, 4th, 6th, 8th, 10th and 11th nerves in conjunction with Deiters' nucleus, the interstitial nucleus, the nucleus of Darkschewitsch and we could possibly add the Edinger-Westphal nucleus to the above. With the last mentioned added we have the sympathetic also. (See Figs. 30 and 33 for the above and for the work of Penfield and Muskens).

Concentration upon the trigeminal nerve in relation to the spinothalamic and other portions of the tract within the cerebrum in the vicinity of the internal capsule is important for not only is this nerve tract related to the parasympathetic system but many of its functions subserve those very importnt to the gastrointestinal tract. As a trophic impulse carrier it has one very important position but as a medium of transmission of sensory impulses from the entire oral and other

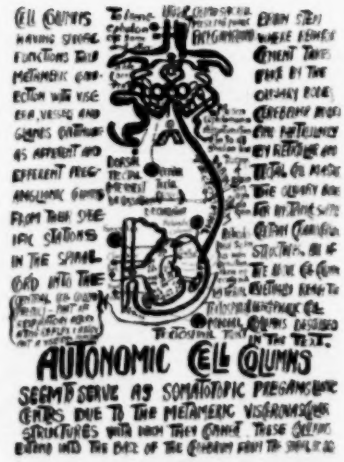
cavities of the face, it has a special extensive function related to the upper gastrointestinal tract. The function of mastication in all forms of vertebrates and particularly the definite localization of rhythmic chewing as centered in the frontal regions makes us realize that the extent not only of the sensory fibres but also of the motor fibres of this nerve is well deserving of attention from both the motor as well as the secretory and the neurogenic control or gastrointestinal tract. Furthermore, its great interrelationship with the other cranial nerves, particularly those concerned with head and neck movements, makes it a very important factor in the internuncial system within the brain stem. In our anatomical illustrations of the autonomic we made diagrammatic references. The actual cellular and fibre structures are much more numerous than we have shown. This is true for the above as well as for the spinal autonomic which contains at least four more possible tracts above the number given by us. The course of this trigeminal pathway (Kappers, Huber and Crosby) shows that almost at all levels within the brain stem and cerebrum this pathway is so situated as to make many nuclei, including those of the central autonomic, susceptible to connections with it.

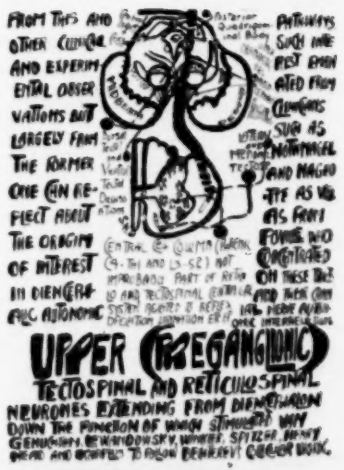
Although Archambault and Fromm did not devote as much space as they might have to the development of this pathway, their inclinations towards the presentation of a great deal of clinical material and references in their monumental work to which we are referring, indicate, that they placed a great deal of confidence in this pathway and in the trigeminal nerve in particular as an important structure related to trophic functions along the final common pathway. The reader will realize that as in gastrointestinal control by the diencephalon we confront the mammillothalamic and dorsal longitudinal fasciculus tracts as against the spinothalamic in the problem of trophic control. The trigeminal theory deserves more emphasis since anatomically, besides belonging to the spinothalamic it also belongs to the cranial nerve chain whose internuncials are intimately bound with the medial longitudinal autonomic system of the brain stem. Thus Archambault and Fromm state that the trigeminal theory in relation to trophic impulses receives strongest support from the histologic observation in the case of Mendel and that of Loeble and Wiesel. They state that the so-called neuralgic pains which are common enough were said by Cassirer, Marburg and many others almost never to have the intensity of the pain occurring in trigeminal neuralgia. Archambault and Fromm claimed that the loss of protective covering resulting from destruction of subcutaneous fat and connective tissue might be responsible for the hyperesthesia and tender trigeminal pains on electrical stimulation of the nerve and muscle. This would detract from the favor of the trigeminal theory. These authors claim that older writers have reported such findings, especially Denig, Estor, Kahler, Mauclaire and Strasburger. In spite of the tegumentary changes, the sensory findings were given definite consideration by such authorities as Marburg, Mendel, Kracht, Heinemann, Donath and Jendrassik, Sachs, Krueger and Boenheim, Boguslawski, van Bogaert, Helsmoortel and finally Stiefler. Muscular atrophy involves therefore an extensive anatomic problem.

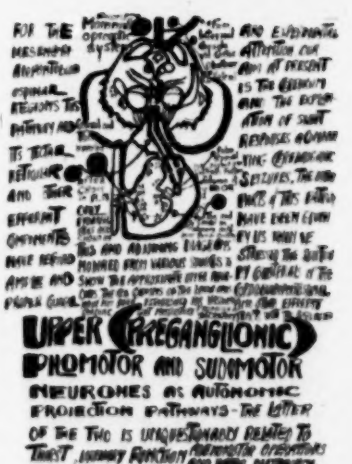
Although, in the course of our presentation of the data of Archambault and Fromm on the sympathetic within the brain stem as well as upon the trigeminal nerve and the elaboration of references which we have given we did not repeatedly stress the terms of centrifugal and centripetal, we implied the same, and our presentation of motor, and sensory findings definitely meant such terms. The purpose of reminding the reader of these particular terms is because Spiegel made it a definite point to stress centrifugal and centripetal in the presentation of his own matgrial and in the references to the literature which he offered in dealing with the spinothalamic tract in relation to neurogenic gastrointestinal control. The literature of Archambault and Fromm almost entirely falls into the category of the data presented by Spiegel. The material of the latter deals however with more experimental than clinical data. The location of the tracts in Fig. 39 proves this.

Although in all of the above discussions we dwelt largely on the subject of trophic tracts and must have seemingly strayed far afield from the subject of the mammillothalamic tract and particularly from our proposed neurogenic control of gastrointestinal function, we have really not been away from the subject as far as one might imagine. We have repeatedly emphasized the fact that Watts and Fulton as well as Spiegel showed that certain areas within the cerebral cortex subserving gastrointestinal functions also control those of the musculoskeletal system. If not within the same area of the cerebral cortex, the areas were very near each other in which the levels of the body occupied by the control of either the smooth muscle neurogenic functions or the skeletal and osseous structures. Both were concomitantly affected by lesions in which one or the other was produced. For this reason the muscular atrophy seen in cases in which the spinothalamic tracts or the pyramidal tracts were affected is expected to involve smooth muscle structures at the same levels. These smooth muscle structures under consideration would therefore fall as far as their neurogenic control was concerned either into the gastrointestinal group or the urinary system.

Archambault and Fromm state that, as a rule, the atrophic process in progressive facial hemiatrophy involves all the structures of the face; the skin, subcutaneous fat and connective tissue, and muscle as well as bone. That the skin may escape entirely or that the subcutaneous fat and connective tissue may disappear before or without concomitant involvement of the skin, has been emphasized by Marburg and Wartenberg in whose combined statistics fully 15 such cases are mentioned. As regards the so-called muscular atrophy, Marburg correctly pointed out that it is due essentially to the disappearance of connective tissue components of the muscle as is well shown by the retention of the functional activity and the absence of qualitative changes in the electrical reactions. This is true not only of the masticatory and of the facial muscles but also lingual and palatal musculature which not uncommonly participates in the hemiatrophy. Cartilage seems to be involved in the following frequency in cases showing progressive facial hemiatrophy: nasal, auricular, laryngeal and tarsal. The nasal seems to be far outstripping the other in the frequency of involvement.


AUTONOMIC CELL COLUMNS
SEEM TO SERVE AS SOMATOTOPIC PREGANGLIONIC CENTERS DUE TO THE METAMERIC VISCERAL AFFERENT STRUCTURES WITH WHICH THEY CONNECT. THESE CELLS EXTEND INTO THE BASE OF THE CEREBRUM FROM THE SPINAL TO





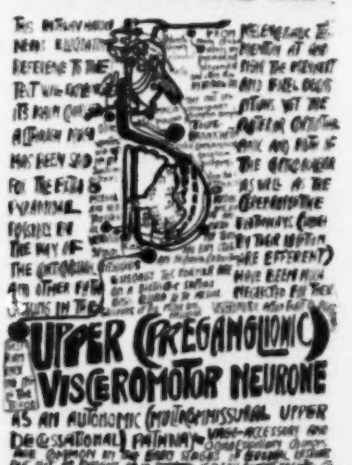
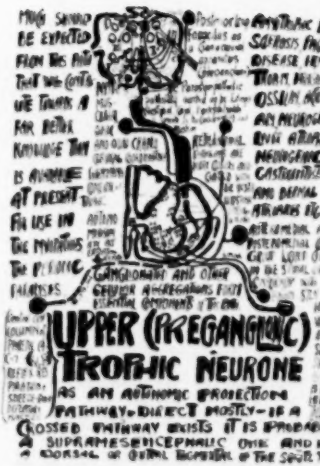


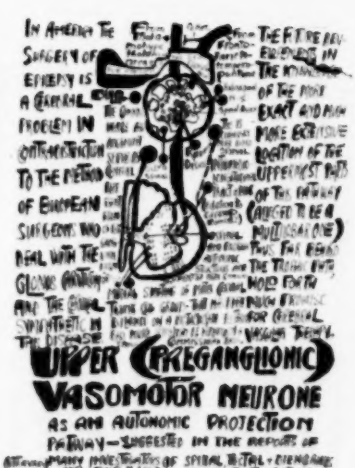
Fig. 43—Top left, Fig. 44—Top center, Fig. 45—Top right, Fig. 46—Bottom left, Fig. 47—Bottom center, Fig. 48—Bottom right.

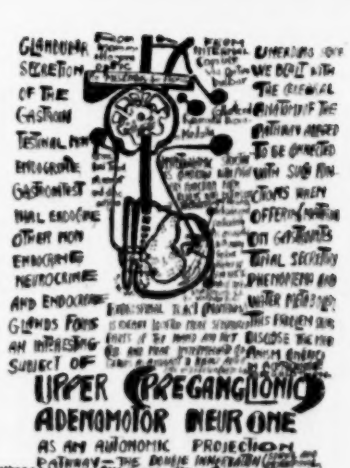
The data given above on the musculoskeletal system covers, as is well known, not only the peripheral structures which are responsible for progressive muscular wasting, but also the central brain stem, hypothalamic and particularly the pyramidal and related pathways which subserve muscular and related structures in the musculoskeletal system. The cases which Archambault and Fromm presented from their own collection, however, do not fall into the last mentioned category. The literature which they present, is on the other hand replete with instances of final common pathways structure lesions in which is produced progressive muscular wasting. In neurology in general, but in epilepsy in particular, we have encountered muscular atrophy most often contralateral to a cerebral lesion which has become atrophied secondary to traumatic, infectious, embolic or other processes. The diminution of muscular chondral osseous or adrenal elements is contralateral to that of the location of the diminished neural elements (Fitch, Weingrow and Pigott, 1938-1941). Such body wastings or hypogeneses are the result of cerebral involvement in a number of places but occur mostly when regions subserving motor function are eliminated by pathological processes.

In regard to the wasting of the bony element it has been emphasized by Cassirer, Marburg and others that it is directly proportional to the age at which the atrophy has its onset and that the pronounced atrophy is surprising in a process electively affecting younger persons before full development of the bony framework has been reached. Marburg mentioned Rothmann's case as apparently the only exception up to the time of his monograph. Archambault and Fromm state that atrophy of the bones of the face in cases developing after the age of 20 years was specifically mentioned by Boguslawski, Krueger, Roger, Reboul-Lachaux and Montagnier, Cerni, Mauthey and Wolff. Throughout this work we had in mind atrophy of smooth musculature of the intestinal tract. The gastroenterologist is probably more qualified than we to elaborate upon a subject as interesting as that. The neurogenic mechanism involved in such a phenomenon is probably the same as that which operates in musculoskeletal and osseous atrophy. Why most investigators in neurologic gastroenterology lay all stress upon the motor and relatively neglect the trophic aspects of smooth muscle we do not know. The work of N. D. C. Lewis on vascular muscular hypogenesis seems related to the above.

In the original quotation from Archambault and Fromm which we presented in this paper there has been data to point to the fact that the question came up as to whether the fibres of the sympathetic located along and supplying the blood vessel were the same fibres to which trophic functions could be assigned. If this question came up with regard to the peripheral, there is no reason why it should not include the central and therefore the pyramidal and spinothalamic elements. In relation to the above it is noteworthy to state that Stavraky in his experimental work on animals, while working on the interpeduncular region, also stimulated the optic thalamus and obtained definite evidence that it is also a center of vasomotor control. The unstriped muscle needs as much representation as the striped.







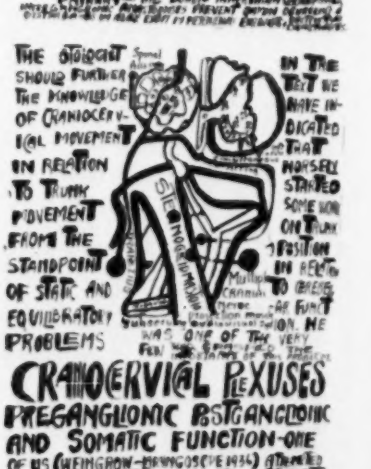


Fig. 49—Top left, Fig. 50—Top center, Fig. 51—Top right, Fig. 52—Bottom left, Fig. 53—Bottom center, Fig. 54—Bottom right.

Muscular wasting, though occasionally found independent of vascular and other sympathetic dysfunction was in a large percentage of cases associated with it. The important point to stress in the above is the fact that such a relationship was noted in central as well as in peripheral types of lesions. Dissociation of sensations that came from the same pathways is the rule in the last mentioned type of lesion while with capsular lesions or spinal syndromes, all the functions of a pathway disappear with damage to the same. As far as connecting the anatomical regions of the mammillothalamic or final common pathway with the problem of musculoskeletal systems or in other systems indirectly through the references of Archambault and Fromm, it might be remarked now that a great deal of space could be devoted were we to consider every theory or even some appreciable parts of them. We have, however, no time at present to dwell upon any other of the theories besides those we cannot help remarking about. The sclerodermal and endocrine theories we have to completely omit and regretfully so, particularly the last mentioned which is evidently very relevant. The only theory besides the trigeminal one, which we have already stressed, is the sympathetic theory of progressive facial hemiatrophy. Archambault and Fromm, state that Stiefler, although admitting that his case agreed with the trigeminal theory of Mendel, Loeble and Wiesel, nevertheless maintained that the hemiatrophy results from involvement not only of the trigeminal fibres but of the parasympathetic fibres which course with them. It likewise may be stated that, aside from a large part of the vasomotor fibres which do travel in the periarterial sheaths, the secretory, pilomotor and oculopupillary components of the cervical sympathetic, according to Langley and André-Thomas, after emerging from the superior cervical sympathetic ganglion pursue their course in the carotid plexus and join the trigeminal trunk at the gasserian ganglion and remain inherent components of its three peripheral divisions. Archambault and Fromm claimed that the sympathetic theory was originally proposed in 1875 by Seeligmuller who dealt with the cervical sympathetic. Seeligmuller was followed by Jaquet, Bouveyron, Oppenheim and countless others. Archambault and Fromm claimed that they regarded the sympathetic theory as the only valid one since it has the great advantage of being supported by the known facts of anatomy and pathology as well as of clinical observation. They state that Marburg, who was skeptical because the sympathetic disturbances so frequently recorded indicated in some cases an irritative and in others a destructive process, nevertheless mentioned with admirable sincerity a very large number of observations definitely favorable to the cause of the cervical sympathetic as being related to chronic progressive facial hemiatrophy. He referred to ten authors who observed mild exophthalmos and widening of the palpebral fissures. He also referred to six clinicians whose patients suffered from full fledged Horner oculopupillary syndrome and to seven other clinicians whose cases presented sensitive or swollen cervical sympathetic ganglia on the affected side. Among the authors mentioned as connected with the above theory are Heiligenthal, Ascher, Kurt Mendel, Oppenheim, Claude and Cantraine and finally Cassirer. The last men-

tioned author was the great advocate of an unlocalizable lesion of the vasomotor system. He reported a typical instance of facial hemiatrophy which developed in connection with a malignant tumor of the third to fifth cervical vertebra. Structures having a peripheral innervation are in most nervous system conditions affected in many similar ways if lesions, located above the peripheral neurones, occur. This is true not only in the case of the above organs but in structures subserving gastrointestinal and water metabolism functions. In cases of epilepsy the lesions are, however, mostly central instead of peripheral, and these, as will be shown in our cases, are usually corticodiencephalic. Other authors that concurred in this theory are Bruning and Stahl, Cerni, Trommer and finally Mauthey. Ingelrans, Dejerine and Krebs, Trabaud, Roger, Reboul-Lachaux and Montagnier as well as Jelliffe and White and others favored the sympathetic groups within the brachial plexus as a center of atrophy in the muscular control.

Throughout the entire presentation of the neuroanatomy of the cortical diencephalic system we have had little occasion to refer to the problem of epilepsy except in connection with the mechanism of tonus. Some references were given in the course of our dealing with spasmodic lateral conjugate deviation of the eye and head movement in an epileptic. In the discussion of that paper, however, the problem of epilepsy was brought up by Rosett who claimed that the spasmodic conjugate deviation as presented by Davison and Goodhart in their case was a phenomenon connected with epilepsy. Whatever was said in relation to epilepsy was done largely on the basis of results of cortical stimulation of various areas. Here and there was a reference to the oculopupillary reaction as taken from the literature; even in the Davison and Goodhart exhaustive analysis. There was hardly anything in the entire literature dealing with the mammillothalamic system as such that specifically referred to epilepsy. The Brissaud-Vivoldo syndrome as shown by Archambault and Fromm referred to the periventricular system and therefore to the supraoptic tracts which enter the thalamus producing the central pain syndrome via the hypothalamus. This route is evidently not identical with the mammillothalamic pathway but near it. Some reference was also made to the work of Morgan who showed some cellular changes in the hypothalamus of epileptic patients and even in psychotics as anticipated by N. D. C. Lewis.

The material dealing with the subject of epilepsy in relation to trophic muscular phenomena in the work of Archambault and Fromm is therefore doubly important to us. In the first place, with the data from the above writers, the muscular atrophy or hypogenesis which we will present in our papers will have the backing of the literature. We first drew attention to this fact in epileptics as a phenomenon which forms part of cortical pathology in our first report of our institutional cases in 1938. Aside from the above, the reference to the anatomy of trophic tracts within the cerebrum will add another approach to the gastrointestinal and urinary neurogenic problem. This, coupled with autonomic reaction occurring in the pupils and manifestations in other parts of the body in the course of an epileptic seizure, should present a series of combined issues necessitating a

final decision upon a definite cerebral autonomic tract which would involve the frontal, paracentral and cingulate.

Archambault and Fromm presented rather detailed descriptions of the occurrence of epilepsy in relation to progressive facial hemiatrophy. The occurrence of muscular atrophy in conjunction with epilepsy, whether of the so-called idiopathic and generalized forms, or of the Jacksonian type is more interesting than one might imagine. Wartenberg, whose patients exhibited both conditions although the seizures were predominantly Jacksonian, unequivocally expressed the opinion that there is more than pure coincidence between the two and erected a most elaborate hypothesis to affirm his position. Although our long standing experience in epilepsy does not lend itself to agreement with Wartenberg's views on the congenital phase we fully agree with him on the diencephalic stand. We must admit that Wartenberg has shown himself by the above to favor a central autonomic, somatotopic system which is the guiding light of every neurologic clinician. That aim alone is justifiable. We might add furthermore that he did so before the age of our modern pneumoencephalographic methods. The pneumoencephalograms in our cases (Fitch, Pigott and Weingrow, 1938-1941) confirm Wartenberg's position because of the occurrence of dilated third ventricles in many of our cases. We regret that we cannot here furnish the full details of his theory but the essential feature is that facial hemiatrophy is a primary clinical manifestation which would result from a lesion of the higher vegetative centers in the diencephalic floor, that sympathetic innervation disturbances would soon affect the vasculature of the homolateral cerebral hemisphere and thus predispose the hemisphere to consequent toxic or infectious invasions which would account for the occurrence of contralateral seizures in the contralateral extremities. The scope of this region is shown in Figs. 30 and 55.

We realize that throughout our paper on the subject of the neurogenic control of the gastrointestinal tract and of the localization of autonomic phenomena we have been guilty here and there of digressions. Sometimes digressions might be considered irrelevant. The reader must remember, however, that our interests are primarily those of epilepsy. In this condition we have throughout two decades made observations not only upon the vegetative system but also upon certain other characteristic neurological findings. We therefore digressed now and then to impress the reader with the fact that epilepsy has a neurology in its own right. We emphasized the neurological findings of Gowers, Oppenheim and those of Brown-Sequard. Far be it from us to champion the cause of neurology in epilepsy. We feel that there are far better neurological clinicians than we to undertake such a herculean task. Muskens did so rather ineffectively because he was primarily a neurophysiologist. It is, however, humility and regret that we feel towards Archambault. The neurology of epilepsy misses such an outstanding figure who was the pupil of Charcot. We feel that Archambault would have done a great service to the cause of epilepsy had he elaborated more on this subject. He was probably up to date not only on the neurological findings given by the authors mentioned

above but also on the views held by and on the fine clinical descriptions of Spiller. With a keen eye for the literature which he possessed there is no doubt but that he was aware of the writings of L. P. Clarke and of the literature on exhaustion-paralysis, etc. in epileptics. Archambault might have chosen to avoid stressing the neuropathology of epilepsy as a basis of muscular atrophy because in doing so he would be forced to sacrifice other parts of his illuminating paper. He touched upon trophic mechanism and gave us the most thorough account of this subject known in clinical neurology. Evidently his interest in epilepsy did not surpass that which he had in other outstanding subjects in neurology.

It might be, however, that some other outstanding clinicians such as Wartenberg, who is interested in the subject of muscular atrophy would some day within this generation resume this topic in relation to epilepsy so that another very

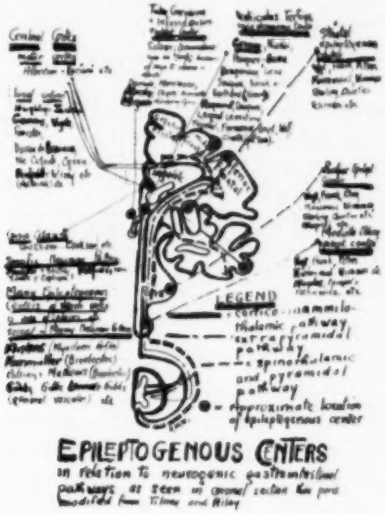


Fig. 55

important function of the vegetative nervous system might receive special consideration because of its rather common occurrence in focal and general epilepsy. Although the neurology of epilepsy has, as pointed out by Muskens, various other neurologic syndromes such as fleeting anesthesia, segmental sensory disturbances, remittent reflex changes, permanent cranial nerve findings such as paralysis of extraocular musculature, inequalities in the pupils, and definite cortical motor and cortical sensory changes as pointed out by the studies in the cortex by Henry Head, none of these are as important as the muscular atrophy related to the autonomic features of the convulsive mechanism. Compare the legends in Figs. 39 and 55.

We must confess that although our interest has been on and off during the past decade directed to the central autonomic nervous system and that we were aroused to the dilations of the third ventricle in a rather large percentage of cases,

yet we were so much interested in the neurology of epilepsy in general and in the neurological problem of correct cortical localization in particular, that we failed to stress the trophic aspects. Though we have repeatedly observed definite evidences of neurological disturbances pointing toward the autonomic nervous system not only in relation to attacks, but as definite phenomena in the course of the routine coordinative, reflex, endocrine, and cranial nerve examinations such as pupillary inequalities, endocrinopathic hemiatrophies and neurogenic sclerodermal conditions (Tracy's white spots), etc., yet we have never attempted to classify the autonomic manifestations and group them in the form of syndromes that might point to involvement either of the mammillothalamic tract region or the final common pathway or even of the spinothalamic fibre system. We can say however throughout our experience with the detailed neurological examinations of epileptics we have invariably felt that the problem of dissociation of Henry Head was neglected. Head dealt largely with cortical dissociation of sensory phenomena. He did not stress modification of sensory impressions by the thalamus. We however found an appreciable amount of sensory modification in epileptics. It is felt by us that some of these, particularly if associated with autonomic imbalance are of thalamic origin. It should be remembered that the lateral division of the dorsal thalamus distributes fibres to almost all lobes of the hemisphere and is intimately bound with the olfactovisceral portion of this structure. Its influence on the neurogenic control of gastrointestinal function and possibly on trophic phenomena is not impossible. We have taken cognizance of his monumental investigations into sensation of a cortical type and dissociation has been applied to motor and trophic phenomena. It is surprising that such syndromes as have been pointed out by Archambault and Fromm and connected with the autonomic did not receive much greater attention in epilepsy thus far. Not only during our presentation of data in the literature in 1938 did we stress the fact that just as there are other positive neurological findings there are also manifestations of trophic involvements in the form of muscular atrophy of a corticogenic nature, but in later publications we also reiterated that fact (Fitch, Pigott and Weingrow, 1939), (Pigott, Weingrow and Fitch, 1939-1940). We urge the reader to refer to the last mentioned publication. Here we took great pains to relate in detail some of our findings on the autonomic nervous system in general, in the gastrointestinal and urinary tracts in particular, and coordinated all findings upon etiologic, pneumoencephalographic, seizure frequency and other data with the autonomic manifestations of cranial nerve disturbances such as pupillary inequality and definite wasting of the body musculature as a result of lesions within the cerebral cortex. We did not stress the diencephalon because of the preponderance of fragmentary unilateral findings over complete hemianesthesias, hemiplegias and hemiatrophies. The last mentioned types of findings would be the only ones pointing to deep structure involvement.

Although the last mentioned article on the subject of epilepsy has been the most extensive in a series of papers giving various installments in one of the journals and embracing almost the entire field of epilepsy from the detailed presentation of the literature from the result of cortical stimulation to autopsy

findings in a large number of cases, we nevertheless failed to concentrate upon solid neurological findings in relation to the autonomic nervous system as we did in a subsequent publication. The paper which was published in 1941 (Weingrow, Fitch and Pigott) contains positive neurological findings along the entire field of the neurological examination scheme, but in addition stresses some of the muscular atrophy of a corticogenic nature, and mentions definite pupillary inequalities that occur independently or are associated with other cranial nerve findings as residual paralysis and dissociations of a cortical and subcortical type, thus creating autonomic syndromes in which one extremity may be paralyzed or wasted and with it there may be a pupillary change or some other manifestation of autonomic imbalance. We do not wish to create new syndromes ourselves, but out of such an accumulation of grouped data others can and should do so. We feel, however, that in all the writings of such a great neurologist as Archambault and in those of the industrious Wartenberg as well as in the syndromes of total hemiatrophy thus far accumulated, there has been no special attention to the creation of a pure cortical autonomic syndrome. Most authorities who wrote upon the trophic phenomenon of muscular wasting in relation to all the diseases that Archambault and Fromm mentioned in their paper, (and there surely are many of them from multiple sclerosis, syringomyelia, congenital atrophies, syphilitic brain lesions, to even vascular disturbances in the brain), no one has ever decided to show that one does not need a complete hemiplegia or a complete hemiatrophy to be associated with other autonomic manifestation disturbances as a result of involvement of the cortical or subcortical portion of the cerebrum. In fact, paralysis of one extremity either of the upper, or lower, can be associated with muscular wasting as the result of a lesion, cortical or subcortical, within the frontal, or other portions of the brain and have all the earmarks of involvement of the autonomic nervous system particularly if such a lesion is associated with pupillary changes and surely if a combination such as the above is situated in an individual who suffers from an epileptic attack with its galaxy of other autonomic paroxysmal and preparoxysmal and neurogenic gastrointestinal, urinary or other system disturbances. See Figs. 30 and 33.

Throughout our neurological contributions to epilepsy in the last ten years it may be noted that we concentrated mostly on the cortical and subcortical regions of the cerebrum. In our findings, however, whether with the cranial nerves or in the muscular wasting as far as the neurogenic control by the autonomic nervous system is concerned, these syndromes invariably fell into either the hypothalamic, preoptic, tuberal, mammillary, thalamic region and then along the frontal region radiating from the thalamus thus constituting the mammillothalamic or mammillopreoptic system. We saw little along the lines of extrapyramidal system manifestations in epileptics except possibly in the rigidity of neurosomatic deteriorated cases and in rather uncommon cases of athetosis associated with epilepsy. For this reason and others we lean away from Watts and Fulton's favoring the extrapyramidal system as one that exerts neurogenic control of gastrointestinal operations. We can see into their anatomic conclusions, because the prefrontal

region has a cortical extrapyramidal center. We can also subscribe to the fact that there is a thalamostriatal system and that the hypothalamus has a nigral pathway but these are not enough considering the fact that the mammillothalamic, the habenular and preoptic regions, have been proved to have neurogenic gastrointestinal influences much more so than the striatum or substantia nigra. When an isolated syndrome pointed largely to the autonomic region accompanied by cranial nerve findings exclusively, the above group was assumed as implicated. Most of our cases, however, fell into the pyramidal and spinothalamic varieties of neurogenically controlled autonomic manifestations. The last mentioned group included pyramidal tract findings such as exaggerated reflexes, sensory cortical dissociation, and atrophy together with the autonomic syndrome. We have, therefore, in our material favored the pyramidal and spinothalamic group. Our findings, though distinguished from those of other authors because of monoplegic and monoatrophic instead of the total hemiatrophy of the Brissaud-Vivoldo type as given by Archambault and Fromm, nevertheless eventually lined up with the experimental and clinical material presented by Watts and Fulton, Watts and Frazier, Bechterev, Spiegel and associates, and finally Rosett. Before continuing with Archambault and Fromm we wish to stress one more physiological fact. It concerns the difference between the authors just mentioned and Watts and Fulton as far as the extrapyramidal system is concerned. Whether we deal with trophic disturbances or motor upsets of intestinal musculature it should be remembered that our chief interest is the diencephalon and cortex in relation to viscera. The four authors were well aware of the pyramidal system and extrapyramidal as well as all the spinothalamic afferents. Yet Archambault avoided the rubrospinal thalamic connection and the extrapyramidal, and failed to mention even the reticulospinal, tectospinal, ground bundles or bulbospinal system.

Further analysis by Archambault and Fromm shows that the above is true and that other conditions that are related to epilepsy such as migraine is brought into the picture. The last mentioned authors state that up to 1925 Wartenberg had collected only four cases of generalized and four cases (including his own) of Jacksonian epilepsy. Since that date Archambault and Fromm had found three additional cases, those of Lauber and H. G. Wolff and our one case, all of which exhibited generalized seizures. This brings the total number up to eleven and Archambault and Fromm had no doubt that Wartenberg, like themselves had overlooked some cases. Nevertheless they thought that there is nothing astonishing in the fact that rare as it is, facial hemiatrophy should occasionally appear in a person suffering from so common a disease as epilepsy. Again the clinical mastery of Archambault comes to the fore with our statement that in ten years we have jointly observed over 300 cases of hemiplegic epilepsy in whom total hemiatrophy occurred in at least over 50 per cent of the total. The above statement of Archambault and Fromm will give the reader an idea when the following statistical data is presented by the same author.

Such cases, even admitting that the count of Archambault and Fromm falls short, is still too insignificant when one remembers that the total number of cases

of facial hemiatrophy thus far recorded probably exceeded about 400. Again, it is well to bear in mind that not all cases of so-called Jacksonian epilepsy indicate a focal cerebral lesion according to Archambault and Fromm. The most alluring fact in connection with the problem is that in the majority of the eleven cases referred to, the convulsive episodes appeared some time after the hemiatrophy had become definitely recognizable. In this respect the literature would substantiate Wartenberg's views. The conclusions drawn from the above are self-evident in relation to our remarks prior to the continuance of the data by Archambault and Fromm. Archambault and Fromm failed to stress the fact that in total hemiatrophy the atrophic process is stationary rather than progressive. A large percentage of the cases which we will eventually offer also falls into this group. Moreover, our cases of epilepsy suffer from the muscular atrophy of the partial residual arrested or even the hypogenetic type. These include chondral and osseous structures.

Archambault and Fromm further state that migraine, a close relative of epilepsy has been encountered repeatedly in connection with facial hemiatrophy and Wartenberg mentioned six cases exhibiting this association. The neuroanatomic approach which is occasionally seen among internists and in pursuers of the specialties that require some neurologic training seems a valuable asset in subjects such as migraine, Ménière's disease, etc. In such conditions vomiting occurs rather often. Invocation of the diencephalic pathways or those connected with operations of the vestibulotectal and cerebellotectal structures to explain the nausea and vomiting or even other gastrointestinal reactions should present an interesting subject. Archambault and Fromm add that it has already been pointed out that Reiss and Bourguignon presented such cases. They go on further to state that the occurrence of tonic or clonic spasms of the facial masticatory or lingual musculature had already been mentioned and that in the recently reported case of Kirschenberg there was a frequently recurring trismus. Here again was Archambault's chance to approach the extrapyramidal via the dentorubral and rubrothalamic pathway but he avoided it. Although these pathways enter the thalamus and could be connected with its olfactovisceral component and thus related to trophic phenomena Archambault and Fromm said nothing about it. They probably knew that they were treading on dangerous ground. The thalamus which modifies all afferent impulses from the photoelectric impulses of vision to the vibratory ergastic components of auditory impulses probably also has centers that transform chemical impulses from the viscera as they do olfactory and gustatory afferents into bioelectric phenomena as an array of sensations from the viscera and tissues.

The data of the main authors under consideration Archambault and Fromm, in so far as they relate to the neurogenic cerebral control of the phenomenon of progressive muscular atrophy and to the spinothalamic and pyramidal as well as the mammillothalamic system may be found in the following final short quotations:

It is our conviction that the sympathetic theory and the autonomic (Fitch, Pigott and Weingrow) alone, affords satisfactory explanation of the great majority

if not the totality of cases of facial hemiatrophy thus far recorded. This opinion is based on the following facts, all of which are well established on either clinical pathologic or anatomic grounds.

Archambault and Fromm present seven points to prove their contention. Of these we include point number 2 and point number 7 since these apply to our data more than the others.

"In the group of so-called symptomatic hemiatrophy (syringomyelia, hematomyelia, brachial plexus injury, bulbopontine foci of encephalitis, etc.) a concomitant Horner syndrome occurred in the majority of cases, and not infrequently there were vasomotor and secretory disturbances as well."

"While the preceding paragraphs apply to the cervical sympathetic alone, (not the autonomic, Fitch, Pigott and Weingrow) the total hemiatrophies are to be explained by the perfectly logical hypothesis of Brissaud and his pupils who incriminated a lesion of the fibre pathways coursing in the periependymal zone of the fourth ventricle and Sylvian aqueduct, presumably fibre tracts located in the proximity of the motor nuclei of the cranial nerves (such as the 'fasciculus longitudinalis dorsalis of Schütz'), the mesencephalic route of the trigeminal, the area adjoining the descending spinal root of the same nerve and the fasciculus solitarius."

The only change we wish to make is the addition of two other fibre tracts as shown with our description of the basket on a tripod. The mentioning of the fasciculus longitudinalis dorsalis of Schütz in relation to vegetative functions threw an anatomic flare into our concepts of the relation between gastrointestinal trophic and motor and musculoskeletal trophic phenomena. All along the analysis of Archambault and Fromm's material we felt that they had neglected the combinations of the mammillothalamic, the hypothalamic and the preoptic systems consisting of Meynert's, Ganser's and Gudden's commissures. We were bent on taking them to task for that. Now we see how they have united gastrointestinal trophic motor and secretory phenomena and placed their control in the base of the diencephalic region by innuendo.

For the remainder of the literature on this subject of trophic tracts in relation to progressive facial hemiatrophy we refer the reader to our bibliography. The material by Archambault and Fromm therefore adds extensively to the data on the spinothalamic and pyramidal neurogenic cerebral control of the autonomic system which includes gastrointestinal and urinary functions. The above writers therefore extensively added to the material missed by Watts and Fulton, Watts and Frazier, Spiegel and Bechterev and the data which we referred to by Muskens and Rosett. The material on the trigeminal as referred to us by Kappers, Huber and Crosby adds an experimental touch to the above.

(*To be continued*)

NEWS NOTES

Course in Postgraduate Gastroenterology

The National Gastroenterological Association announces that its course in Postgraduate Gastroenterology will be given at the Hotel Statler in New York City on October 12, 13, 14, 1950.

The course, which will again be under the personal direction of Dr. Owen H. Wangensteen, Professor of Surgery, University of Minnesota Medical School, will cover the following subjects: Diseases of the Mouth; Diseases of the Esophagus; Peptic Ulcer; Diseases of the Stomach; Diseases of the Pancreas; Cholecystic Disease; Psychosomatic Aspects of Gastrointestinal Disease; Diseases of the Liver; Diseases of the Colon and Rectum and other miscellaneous subjects including Pathology and Physiology, Radiology, Gastroscopy, etc.

The distinguished faculty for the Course has been chosen from medical schools in New York City as well as out of town.

For further information and enrollment write to the National Gastroenterological Association, Dept. GSR, 1819 Broadway, New York 23, N. Y.

Annual Convention of the International Academy of Proctology

The Second Annual Convention of The International Academy of Proctology will be held at the Bellevue Hotel in San Francisco, California, June 23, 24, 1950.

The scientific session will consist of the following papers: "Diverticulosis and Diverticulitis" by Edgar M. Scott, M.D., Birmingham, Ala.; "Surgery of Carcinoma of the Colon and Rectum" by Earl J. Halligan, M.D., Jersey City, N. J.; "Skin Covering of the Stoma Following Resection of the Rectum: Its Value in the Cases of Patients with Chronic Diarrhea" by H. A. Springer, M.D., Cincinnati, Ohio; "Psychosomatic Aspects of Proctology" by William Lieberman, M.D., Brooklyn, N. Y.; "Pectenosis, Illustrated by Colored Motion Picture and Lecture" by Manuel G. Spiesman, M.D., Chicago, Ill.; "The Nutritional Management of Patients with Colon Surgery" by Jacob J. Weinstein, M.D., Washington, D. C.; "The Preoperative Management of the Proctologic Patient" by Charles J. Weigel, M.D., River Forest, Ill.; "Diagnosis of Ano-Rectal Fistulæ" by Emma L. Bellows, M.D., Southampton, L. I., N. Y.; "The Thermal Cutting Unit in Proctologic Surgery" by Alfred J. Cantor, M.D., Flushing, N. Y. and "Routine Proctoscopic Examinations of 1,000 Presumably Normal Healthy Individuals" by Caesar Portes, M.D., Chicago, Ill.

The annual banquet of the Academy will take place on Friday evening, June 23, 1950.

Further information concerning the convention and a copy of the program may be obtained by writing to the Secretary, Dr. Alfred J. Cantor, International Academy of Proctology, 43-55 Kissena Blvd., Flushing, N. Y.

In Memoriam

We record with profound sorrow the passing of Dr. Samuel D. Weaver, Member, of Dallas, Texas.

We extend our deepest sympathies to the family of the bereaved.

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CHOLECYSTAGOGUE *and* CHOLERETIC

Proper nomenclature and definition of the action of pharmacologic agents on the biliary tract encourages clear thinking, discourages misrepresentation and aids in the choice of the proper therapeutic agent.

We are grateful for the clarifying and authoritative statement recently made by Ivy (1) regarding the correct application of the terms "cholecystagogue" and "choleretic". It is definitely established now that a *cholecystagogue* is an agent which causes or promotes the evacuation of the gall bladder. Fatty acids (oleic acid) are effective cholecystagogues. A *choleretic* possesses the property of increasing the output of bile. Bile salts and bile acids are most effective choleretics. They *do not* however promote gall bladder evacuation; in other words, *are not cholecystagogues.*

EXICOL by virtue of its oleic acid and bile salts content is both an effective *choleretic and cholecystagogue.* This has been amply proven (2, 3, 4).

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Indications: Chronic cholecystitis, chronic (non-calculous) cholangitis, functional biliary insufficiency and preoperative and post-operative management of biliary tract conditions.

Dosage: Two capsules t. i. d., a. c. Marketed in boxes of 36 and 100 capsules.

1. Gastroenterology 3:54, 1944
2. Am. J. Roentgenol. 19:341, 1928
3. J. Lab. and Clin. Med. 18:1016, 1933
4. J. Lab. and Clin. Med. 19:567, 1934

• *LITERATURE ON REQUEST* •

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A Major Advance in Peptic Ulcer Therapy:

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ENCOURAGING results with Banthine in a group of refractory peptic ulcer patients were reported by Longino, Grimson, Chittum and Metcalf[1] and later in an enlarged series of patients by Grimson and Lyons[2]. Their observations interested other investigators[3-5] who have obtained equally promising results with this new drug.

These early observers[1,2] noticed that symptoms are sometimes relieved as soon as fifteen minutes following the institution of therapy, and in patients with long-standing, intractable pain discomfort becomes mild and intermittent or disappears. Their conclusions regarding healing of the ulcer are based on roentgenographic evidence.

Thorough pharmacologic investigations indicate that Banthine is a potent but safe drug in therapeutic doses. In these studies no abnormality of the blood or urine or other evidence of toxicity was observed.

BANTHINE: THE DRUG

Chemically, Banthine is β-diethylaminoethyl xanthene-9-carboxylate methobromide. Its generic name is methantheline bromide. It should be noted that the xanthene group bears no relation to the more familiar xanthine group of drugs.

A True Anticholinergic

Banthine may be described as a true anticholinergic drug. In therapeutic doses it controls autonomic stimuli which result in the vagotonia characteristic of the ulcer diathesis. This action is effected at

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the ganglions of both the sympathetic and parasympathetic systems and, in addition, at the postganglionic nerve endings of the parasympathetic system alone. Thus, the resulting therapeutic action is that of control of excessive parasympathetic stimuli effecting a consistent reduction of gastric hypermotility and, in most patients, a reduction in the hyperacidity which is commonly associated with peptic ulcer.

ADMINISTRATION

Because of the prominence of emotional or situational stresses in the ulcer patient and because these stresses vary in each patient, it is necessary to adjust Banthine dosage to meet individual requirements. Initial dosage may be 50 or 100 mg. (one or two tablets) every six hours, day and night, with subsequent adjustment to the patient's needs and tolerance. In addition, the usual adjunctive measures of diet, rest and relaxation should be prescribed for at least the first few weeks of treatment.

It is important that the usual high night secretions be controlled. To this end it is recommended that the night dose be taken six hours prior to the usual time of arising. Further, after the ulcer is healed, it is important that the patient be placed on a maintenance dosage schedule if he is to have a reasonable assurance of nonrecurrence. The maintenance dosage may well be approximately one-half the therapeutic dose and no evidence of chronic toxicity has been observed in maintenance dosage although this experience covers only a period of sixteen months.

Patients may report dryness of the mouth, mild degrees of blurring of vision, slight difficulty of urination or gastric fulness; these symptoms usually decrease or disappear on continued medication but if they are severe they may require dosage adjustment. Untoward reactions with Banthine therapy have not been encountered.

More complete suggestions for Banthine administration are available to the medical profession in Searle Reference Manual No. 40.

Banthine is a product of Searle research. G. D. Searle & Co., Chicago 80, Illinois.

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1. Longino, F. H.; Grimson, K. S.; Chittum, J. R., and Metcalf, B. H.: An Orally Effective Quaternary Amine, Banthine, Capable of Reducing Gastric Motility and Secretions, Gastroenterology 14:301 (Feb.) 1950.

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3. Grollman, A.: Pharmacology and Therapeutics, ed. 14, Philadelphia, Lea & Febiger, in press.

4. Dragstedt, L. R.: Personal communication, March 23, 1950.

5. Collins, E. N.: Personal communication, March 28, 1950.

The Therapeutic Advantages of Certain Select Alkaloids of Belladonna as Antispasmodics

For relieving spasm, hypersecretion and pain, Belladenal possesses certain advantages over other antispasmodic-sedatives due to the efficient spasmolytic action of its Bellafoline component. Bellafoline contains only the levorotatory alkaloids of belladonna. These are more potent and selective than other belladonna alkaloids in producing the *peripheral* (autonomic) effects responsible for the antispasmodic value, as distinguished from the undesirable *cerebrospinal* effects.

Studies by *Kramer and Ingelfinger,* (M. Clin. North Am., **Boston No.**: 1227, 1948) demonstrate the highly efficient action of Bellafoline. By balloon-kymograph studies on the human intestine they found that most commonly used antispasmodics are less effective than atropine (standard dose: 1/100 gr.). Bellafoline was the outstanding exception. It surpassed atropine in both degree and duration of action.

In addition, Belladenal contains phenobarbital which augments the antispasmodic effect of Bellafoline by reducing excitability and tension. Thus, Belladenal is valuable in the many spastic disorders that are associated with hyperirritability and anxiety.

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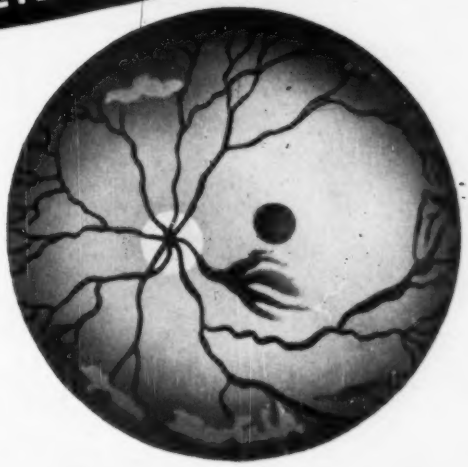

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Accumulating evidence[1,2] is more firmly establishing the ability of inositol to reduce abnormally high blood cholesterol levels. This lipotropic agent activity has been demonstrated not only in patients with liver disease, but also in the presence of diabetes mellitus.[3]

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(1.) Felch, W. C.: New York Med. 5:16 (Oct. 20) 1949. (2.) Leinwand, I., and Moore, D. H.: Am. Heart J. 38:467 (Sept.) 1940. (3.) Felch, W. C., and Dotti, L. B.: Proc. Soc. Exper. Biol. & Med. 72:376 (Nov.) 1949.

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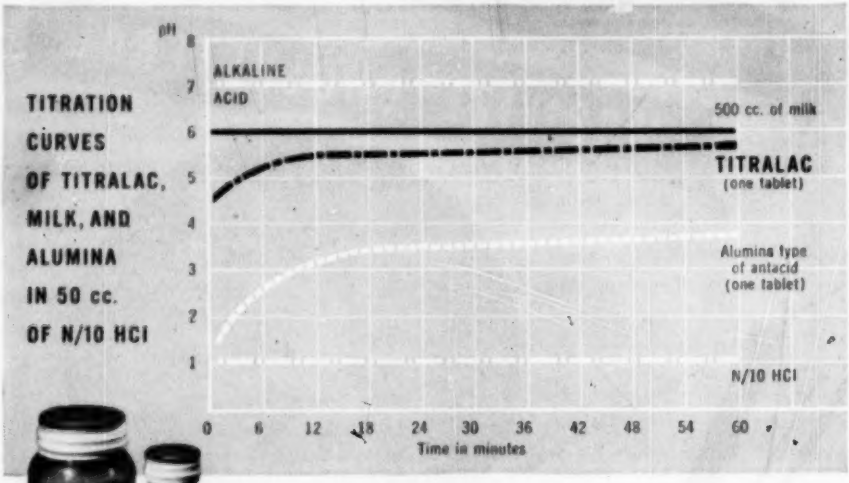

OF PEPTIC ULCER

Gastroenterologists have long endorsed the use of milk, when practicable, for its ideal acid-converting power and buffering capacity.[1, 2] In a recent comprehensive paper, Aaron[3] and others[4, 5, 6] express a preference for calcium carbonate as the antacid to be employed.

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REFERENCES

1. Rossett, N. E., and Flexner, J.: Ann. Int. Med. 18: 193 (1944). 2. Freezer, C. R. E.; Gibson, C. S.; and Matthews, E.: Guy's Hosp. Reports 78: 191 (1928). 3. Aaron, A. H.; Lipp, W. F., and Milch, E.: J. A. M. A. 139: 514 (Feb. 19) 1949. 4. Kirsner, J. B., and Palmer, W. L.: Illinois M. J. 94: 337 (Dec.) 1948. 5. Kimball, S.: in Practice of Medicine (Tice). Hagerstown, Md., W. F. Prior Company, Inc., 1948, p. 210. 6. Special Article: M. Times 76: 10 (Jan.) 1948.

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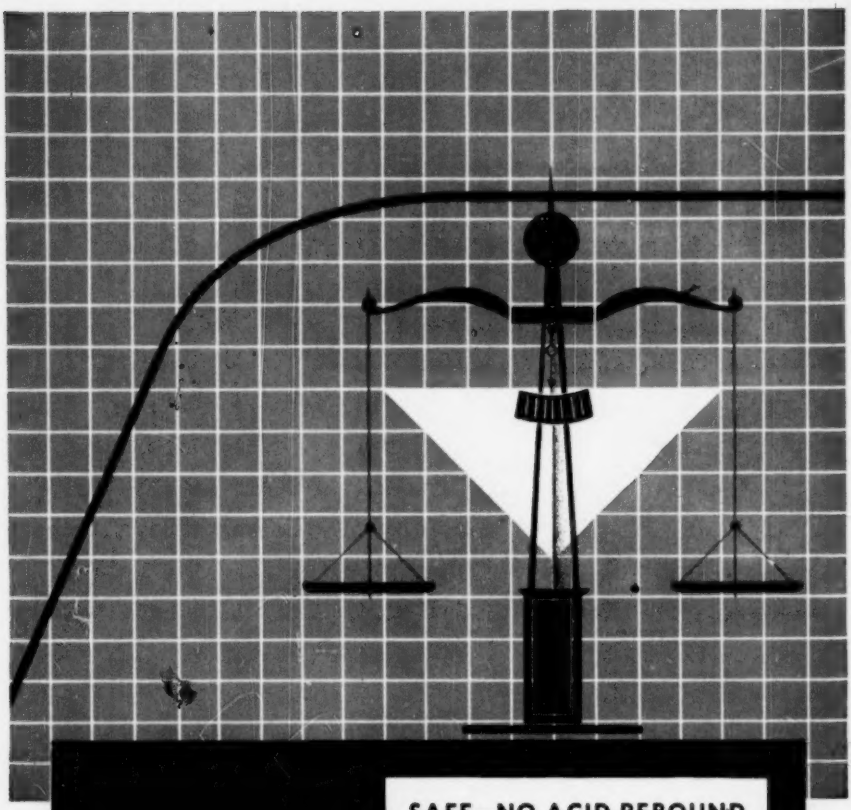

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